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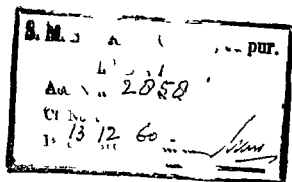
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Society for Vascular Surgery

THE PRESENT EVALUATION OF THE PROPHYLAXIS AND TREATMENT OF VENOUS THROMBOSIS AND PULMONARY EMBOLISM

ARTHUR W. ALLEN, M.D. • BOSTON, MASS.

THERE have been so many epoch making contributions to vascular surgery by members of this Society that I recognize, with due humility, the honor you have conferred upon me by making me your president this year. My interest in lesions of vascular origin has been widespread and still I am fully aware that there are many among you whose accomplishments in this field have been far more significant than mine. It is my hope and expectation that this Society will stimulate research and interest in this important branch of surgery. There are many controversial subjects to be clarified in the better understood disorders of the vascular system and there remain many new approaches to the problems as yet beyond the present scope of therapy.

That I have chosen the subject of *thrombosis and embolism* for this presentation is twofold in origin. The chief reason is that in later years my main interest in vascular lesions has been along these lines, and I therefore freely admit what you already know that is that my competence to discuss any other problem in this field would be questionable. The second reason is that I believe it is appropriate to bring our present data together with a critical eye on the results obtained up to this time. Considering the effort expended in various clinics for the prevention and treatment of thrombosis and nonfatal pulmonary embolism one is at times somewhat doubtful of its comparative value. Statistically it seems possible for the pathologist to show, quite clearly that just as many deaths from pulmonary embolism occur now as was evident ten years ago. On the other hand many clinicians can demonstrate with equal clarity that hundreds of patients are living as a result of their efforts who would have been dead from embolism if left untreated.

William H. Welch the pathologist made early and notable contributions in describing the way and manner in which thrombosis in the veins occurs. It is probable that he interested the physiologist, W. H. Howell in the problem

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and it was the latter who completed research on the chain of substances and sequence of events in the clotting mechanism of the blood. It is also to McLein² working with Howell³ that we owe the discovery of heparin and its antagonistic effect on clot formation, also, the suggestion that this substance if synthesized or purified might be valuable in the prevention of the pathologic phase of thrombosis. Charles and Scott⁴ of the Connaught Laboratories did purify this substance and its action was determined on experimental animals by Murray Best, Jaques and Perrett⁵. Almost simultaneously Murray and Best⁶ in Toronto, and Scandinavian surgeons notably Crafoord⁷ and Ziliacus⁸ stimulated by the chemical researches of Jorpes⁹ in Sweden, began using heparin in the treatment of thrombophlebitis and nonfatal pulmonary embolism. Heparin was expensive and tedious to administer but had the advantages of rapid action and an effective counter agent in protamine¹⁰. Several investigators have reported gratifying results from the use of this agent, and modifications in its administration have been made by Bauer¹¹ and Loewe and associates¹². Reductions in deaths from pulmonary embolism by the use of this method vary from 0 to 16 per cent in comparative series of cases. Bauer particularly has shown that constant and intelligent vigilance of vulnerable patients offers an opportunity for early diagnosis of thrombosis. The results are more spectacular in these early treated patients since cure is more rapidly effected and the number of sudden fatal emboli without warning is reduced. Furthermore the postphlebotic sequelae are thereby diminished.

Homans¹³ was the first in this country at least to call attention to the possibility of preventing recurring pulmonary embolism by interruption of the deep veins of the legs. Also to him we owe the distinction between the type of thrombosis that he termed "bland" from the usually better recognized

interruption of the deep veins of the legs in the prevention and treatment of thrombosis and embolism. This method of treatment is effective is not disabling to the patient, and is admitted by all observers to have a definite role in the proper management of this complication of illness, trauma, parturition and postoperative convalescence. It does on occasion prove of value in an apparently healthy, ambulatory individual whose only complaint is repeated attacks of sudden and often transient pain within the thorax.

To Ochsner and DeBakey¹⁴ we owe the information regarding vasospasm as an enhancing mechanism in the production of thrombosis within the veins. This led them to introduce the
by repeated procaine blocks of
spasm may well account for the

cold climates as compared to warmer zones. This seems further substantiated by the incidence of this disease being at its lowest ebb during the summer and highest during the winter in New England¹⁵. This seasonal variation has also been noted by Crutcher and Daniel¹⁶ in Tennessee with the lowest incidence found to be during the Fall months in material analyzed from the Vanderbilt University Hospital.

Ochsner and DeBakey¹⁷ have further clarified the two types of thrombosis and suggested the term phlebothrombosis to indicate the bland, loose, dangerous thrombus responsible for most of the sudden deaths from massive embolism.

Quick's¹⁸ basic contribution on the prothrombin measurements in the blood has been found so fundamental in the proper management of patients that it deserves special mention. Chargaff, Bancroft, and Stanley Brown¹⁹ using this method in a series of patients demonstrated that all cases of postoperative thrombophlebitis observed during their period of study occurred in those individuals with a prothrombin time lower than normal. That this test was not universally adopted was due to two factors. One was that sufficient skilled laboratory technicians were lacking in most institutions. The other was that at this time no definite plan of proved specific therapy was available. Recently, Mahoney and Rice² have revived and somewhat simplified the routine laboratory examination of every patient in their clinic. They have shown that by this technique they can select for treatment only those patients whose prothrombin time becomes notably reduced during the first postoperative week. If it can be demonstrated that routine laboratory determinations can be carried out on all patients from a practical standpoint, many unnecessary routine precautionary measures can be avoided. I feel that in line with this type of research lies a great future in the management of this problem.

The discovery and synthesis of the inexpensive easily administered and effective anticoagulant Dicumarol, by Link²¹ has brought about a widespread adoption of this drug by many clinicians. The excellent results in comparative groups of patients treated by this method after thrombosis has become manifest are comparable to those obtained by heparin. Notable contributions on this subject have been made by Allen and co-workers²² at the Mayo Clinic. Evans and Dee²³ of the Lahey Clinic, and by several Scandinavian surgeons. Prophylactic use of this drug has also been stressed by Brunzelius⁴ of Stockholm, Allen and associates²² of Rochester, Winn Smith and Mulhgan²⁵ of Boston and others. The dangers from hemorrhage not only in the operative site but elsewhere in the body, particularly in the brain cannot be overemphasized. There are some patients who appear to be particularly sensitive to this drug while others are abnormally resistant. Our present methods of determination of its effect may not be sufficiently reliable since it appears from observations that some patients apparently get some protection from it even though there is no measurable change in the prothrombin level. It is certain to us at least at this time that Dicumarol should never be used empirically and that accurate frequent laboratory determinations should be made until its effect has ceased.

Perhaps we should have given priority in this discussion to the general non specific measures available in the prevention of thrombosis of the veins. Pool²⁶ was the first to call my attention to the importance of routine maneuvers for the prevention of this complication. Many of the pulmonary infarcts that are now so quickly recognized were thought to be due to other causes. Cutler²⁷ was one of the early clinicians to recognize the frequency of infarcts as the chief cause of postoperative chest complication. Pool thought that patients should be turned frequently in bed that abdominal binders were a menace, and that pas

and it was the latter who completed research on the chain of substances and sequence of events in the clotting mechanism of the blood. It is also to McLean² working with Howell³ that we owe the discovery of heparin and its antagonistic effect on clot formation, also the suggestion that this substance if synthesized or purified might be valuable in the prevention of the pathologic phase of thrombosis. Charles and Scott⁴ of the Connaught Laboratories did purify this substance and its action was determined on experimental animals by Murray Best, Jaques and Perrett.⁵ Almost simultaneously Murray and Best⁶ in Toronto and Scandinavian surgeons notably Crafoord⁷ and Zilliacus⁸ stimulated by the chemical researches of Jorpes⁹ in Sweden began using heparin in the treatment of thrombophlebitis and nonfatal pulmonary embolism. Heparin was expensive and tedious to administer but had the advantages of rapid action and an effective counter agent in protamine.¹⁰ Several investigators have reported gratifying results from the use of this agent and modifications in its administration have been made by Bauer¹¹ and Loewe and associates.¹² Reductions in deaths from pulmonary embolism by the use of this method vary from 0 to 16 per cent in comparative series of cases. Bauer particularly has shown that constant and intelligent vigilance of vulnerable patients offers an opportunity for early diagnosis of thrombosis. The results are more spectacular in these early treated patients since cure is more rapidly effected and the number of sudden fatal emboli without warning is reduced. Furthermore the postphlebotic sequelae are thereby diminished.

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So far phlebotomy, thrombectomy when thrombus was present at the level of the highest point of the superficial femoral vein and interruption of the veins at this level have been performed in 1332 patients. About one third of these had had one or more nonlethal emboli. Approximately two thirds of them were subjected to the procedure for positive signs of thrombosis on examination of the legs. A few were operated upon because of a slight concomitant rise in the temperature, pulse and respirations although these patients were symptomless. In this group six patients succumbed to further emboli. Some of these patients were treated with procaine lumbar sympathetic blocks particularly if there was evidence of continued activity of the inflammatory process within the veins. Those who had infarcts after vein interruption were treated also with anticoagulants. A few were subjected to vena cavitation if the emboli continued or were septic in nature. Based on previous analyses of patients with thrombosis of the leg veins approximately 80 deaths would have been expected in this group of 1332.

During the period covered by this study 950 patients were selected for prophylactic superficial femoral vein interruption. These were the older age patients with lesions or infirmities that made them particularly vulnerable to thrombosis and embolism. The operation was done prior to the enforced bed rest of the chief operative procedure, during the main operation or within seventy-two hours of the convalescent period. In this group by comparative data 40 deaths would have been expected from embolism. Four of the patients did die from this cause in spite of the prophylactic procedure.

In 647 patients between the ages of 40 and 60 years 200 mg of Dicumarol were used within forty-eight hours of the operative procedure. If there was no evidence of elevation of prothrombin time within forty-eight hours another dose was given. In some large individuals the initial dose was 300 mg and in some delicate and more feeble patients only 100 mg was given. Occasionally in a particularly resistant patient multiple doses were used. Many of these, however, received only one dose before they became ambulatory and were considered by the danger point. In these 647 patients the percentage of thrombosis was reduced by 80 per cent as compared to the control series. There was some definite evidence of increased bleeding tendency from intestinal suture lines and in large denuded areas such as follow combined abdominoperineal operations. No fatalities from pulmonary embolism occurred in this group of patients but two patients died of hemorrhage in the treated cases. It is fair

sive and later active exercises of the legs were beneficial. To this has been added many helpful features, the most important of these being the elevation of the foot of the bed when feasible, the use of elastic leg bandages, and early post-operative walking. Such general measures can be carried out on nearly 100 per cent of the patients treated in the majority of the hospitals in this country. There are, however, many patients seen in large teaching clinics where the aged, the desperately ill, those with advanced malignancy, and the bedridden cannot avail themselves of these general measures to its full extent. For these more specific methods of prevention of thrombosis must be considered.

It seems obvious now that we should consider the whole problem of thrombosis and embolism in two distinct categories. The first and most logical and the one we feel that should be generally adopted is to direct our interest primarily to the prevention of this complication. This attitude has come about because without it we cannot prevent a considerable number of sudden deaths from massive embolism in patients who give no obvious clinical manifestation that thrombosis of the veins is present. Also there are a minority of cases where the thrombus does not originate in the leg veins but elsewhere in the vascular system. That treatment of thrombosis and nonfatal emboli is reasonably effective by the intelligent use of femoral vein interruption, procaine sympathetic blocks and anticoagulants is well established. It is believed however that in the vulnerable patients, prophylaxis has much more to commend it. It is probable that we would be definitely lacking in duty if the known safe precautions were not adopted in suitable cases. The local aspects of this situation must be kept in mind.

It is now my purpose to present the data on the problem under discussion from the Massachusetts General Hospital up to June 1948. This experience is based on 2929 patients receiving specific preventive or therapeutic measures for thrombosis. These were distributed throughout the hospital in medical and surgical wards and in the private pavilions. It is noteworthy in spite of a very concerted interest in this subject by a majority of the staff that we now find at post mortem as high a ratio of deaths from pulmonary embolism as occurred ten years ago. This is due partly to the fact that few patients now die of shock, infection or pneumonia and live long enough after operation to develop phlebothrombosis. Also there has been a definite increase in the percentage of aged, desperately ill patients admitted to the hospital in the past decade as compared to previous years. The magnitude of surgical procedures has also changed. It is well known that the older the patient the greater the likelihood of thrombosis. Also the character of the disease has a definite bearing on this complication. Patients with trauma to the lower extremities, those with abdominal malignancy, and those with cardiac decompensation are particularly vulnerable to thrombosis and embolism.

The first specific measure carried out was the use of heparin in the treatment of thrombophlebitis. This method did not give the same satisfactory results reported by Murray and Best.⁴ The spectacular effect of phlebectomy, thrombectomy, and femoral vein interruption in the early cases made this the chief method of treatment for a period of years. During this time it was soon

found, if vein interruption was indicated that a bilateral procedure should be done, also that the level of choice was the superficial femoral at its source. The apparently uninvolved vein was often found to be normal and it was interesting to see how little postoperative swelling appeared on this side as compared to the obviously involved extremity. This led to the feeling that there was justification in the use of femoral vein interruption as a prophylactic measure in vulnerable cases. Since there are two identical surgical services it seemed logical to try prophylactic Dicumarol in small doses on one service and use the other as a control. This experience helped us learn how and when to use this drug and gave us definite proof of its value as a preventive measure.

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to say that both of these patients might have died had they not received the drug and in one instance there is little evidence that Dicumarol had any bearing on the subarachnoid hemorrhage occurring within fourteen hours after the administration of 200 mg of the drug

None of the 2282 patients subjected to femoral vein interruption lost his life or his leg as a result of the procedure. Wound infection occurred rarely as did collections of lymph in the operative wound. The follow up studies reveal that none of the prophylactically treated patients had vesper edema on examination one or more years later. In the therapeutic vein interruptions 5 per cent had some evening swelling that was measurable and revealed slight pitting edema. Approximately 10 per cent of these patients in both the prophylactic and therapeutic group complained of night cramps in the legs if they had been unusually active during the day. The procedure did not produce varicosities of the saphenous system. Those who had varicose veins prior to femoral vein interruption were equally divided in their opinions as to whether the superficial varicosities were better or worse after the procedure. Only two patients presented varicose ulcers that had not been present before operation. No patient was disabled sufficiently to interfere with his usual occupation after femoral vein interruption.

CONCLUSIONS

1 A simple quick laboratory procedure is needed to predict which patient needs specific efforts to prevent thrombosis and embolism. The present prothrombin activity determinations require skilled technicians and many of them if all patients are to be evaluated in this manner.

2 A safer anticoagulant drug is desirable. Heparin is expensive and tedious to administer. Dicumarol has the disadvantage of delayed and cumulative action. It should never be used empirically. Frequent laboratory determinations of the prothrombin time are essential during its use. A long weekend with laboratories closed may prove disastrous.

3 The proper use of anticoagulants will result in fewer instances of thrombosis and embolism. The contraindications to their use must be borne in mind. The dangers may outweigh the advantages with improper use.

4 Superficial femoral vein interruption when properly carried out is a safe procedure. This does not produce disabling sequelae. Its disadvantages are that the patient usually has to make an extra trip to the operating room. It does not entirely eliminate further infarcts and it fails to protect a few patients from fatal embolism.

5 Early treatment of thrombophlebitis by either anticoagulants repeated procaine blocks of the lumbar sympathetic pathways or superficial femoral vein interruption hastens the recovery of the disease. These methods eliminate the disabling postphlebotic edema frequently seen in patients who are allowed to recover spontaneously from thrombophlebitis.

6 It is logical that our attention should be focused on the prevention of thrombosis rather than the treatment of the disease after the process has developed. The chief reason for this attitude is that it is the only way to prevent sudden death from pulmonary embolism in symptomless phlebothrombosis.

ADDENDUM

Since delivery of this paper one year ago, therapeutic femoral vein interruption and prophylactic Dicumarol and femoral vein interruption have continued to be practiced with gratifying result. A total of 905 middle age group patients have been given Dicumarol prophylactically following operation with no fatalities from pulmonary embolism and no further fatal hemorrhages. In all 1500 patients have undergone femoral vein interruption as a therapeutic measure and 7 of these have succumbed to postinterruption fatal emboli. There have been 1078 prophylactic interruptions carried out, with 5 postinterruption deaths from embolism. 2,078 patients have been subjected to femoral vein interruptions without loss of life or limb as a result of the operative procedure.

REFERENCES

- 1 Roe Benson and Goldthwaite Joel To be published
- 2 McLean J The Thromboplastic Action of Cephalin *Am J Physiol* 41 200 1916
- 3 Howell W H The Purification of Heparin and Its Chemical and Physiological Reactions *Bull Johns Hopkins Hosp* 42 199 1928
- 4 Charles A F and Scott D A Studies on Heparin *J Biol Chem* 102 433-477 1933
- 5 Murray D W C Jacques I B Ferrett T S and Betts C H Heparin and Vascular Occlusion (Experimental Work Vascular Clotting in Dogs), *Canad M A J* 35 (21) 1936
- 6 Murray G and Betts C H The Use of Heparin in Thrombosis *Ann Surg* 108 163 1929
- 7 Crawford C and Jorpes F Heparin as a Prophylactic Agent Against Thrombosis *J A M A* 116 231 1941
- 8 Zulliacu H On Specific Treatment of Thrombosis and Pulmonary Embolism With Anticoagulant With Particular Reference to the Postthrombotic Sequelae the Results of Five Years Treatment of Thrombosis and Pulmonary Embolism at a Series of Swedish Hospitals During the Years 1940-1943 *Acta med Scandinav* suppl 171 pp 1-14 1946
- 9 Jorpes J Erik The Origin and Physiology of Heparin The Specific Therapy in Thrombosis *Ann Int Med* 27 361-40 1947
- 10 Chargaff F and Olsson K B The Influence of Protamine on the Anticoagulant Effect in Vivo *J Biol Chem* 122 15 1938
- 11 Bauer G Heparin Therapy in Acute Deep Venous Thrombosis *J A M A* 131 196 1946
- 12 Loewe Leo Hirsch E and Cravetz D M The Action of Heparin on Experimental Venous Thrombosis *Surg Gynecol Obstet* 82 225 1946
- 13 Homans J Lower Leg Causing Pulmonary Embolism *N Engl J Med* 94 1914
- 14 Ochsner A S Role of Vasospasm in The Production of Pulmonary Embolism *N Engl J Med* 114 117-124 1940
- 15 Allen A W Linton R R and Donnellon C A Venous Thrombosis and Pulmonary Embolism *J A M A* 128 397-407 1943
- 16 Crutcher R R and Daniel P A Jr Pulmonary Embolism A Correlation of Clinical and Autopsy Studies *Surgery* 23 47-62 1948
- 17 Ochsner A and DeBakey M Therapeutic Consideration of Thrombophlebitis and Phlebotrombosis *New England J Med* 225 207-27 1941
- 18 Quick A J and Leu M Quantitative Determination of Prothrombin *J Biol Chem* 119 1937
- 19 Chargaff F Bancroft F W and Stanley Brown M Studies on the Chemistry of Blood Coagulation *J Biol Chem* 115 149-155 1936
- 20 Mahoney F B and Rice R S Prothrombin Activity—A Diagnostic Test for Early Postoperative Venous Thrombosis *Lect before the American Surgical Association Quebec Canada May 25 1948*
- 21 Link K L The Anticoagulant From Spoiled Sweet Clover Hay The Harvey Lectures Vol 20 Lancaster Pa. 1943 Science Press Printing Company 162-16
- 22 Allen F A Hine E A Jr Krake W F and Barker A W The Use of Dicumarol *Ann Int Med* 27 371-381 1947
- 23 Treatment of Postoperative Venous Thrombosis *England J Med* 238 1 1948
- 24 dies on Its Prophylactic and Therapeutic Acta chir Scandinav (Supp 100) 92
- 25 Smith Geo A S and Mulligan W J Dicumarol Prophylaxis Against Venous Thrombosis in Women Undergoing Surgery *Surg Gynec & Obst* 86 461-464 1948
- 26 Pool E H Postoperative Treatment *New England J Med* 201 510 1929
- 27 Cutler E C and Hunt A M Postoperative Pulmonary Complications *Arch Surg* 114 1920, Postoperative Pulmonary Complications *Arch Int Med* 29 449 1922

THE MANAGEMENT OF RECOVERY FROM VENOUS THROMBOSIS IN THE LOWER LIMBS

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THIS report is based upon a study of fifty five cases exhibiting the quiet stage of venous thrombosis or phlebothrombosis in the lower limbs. It was hoped to learn how the management of the immediate and remote convalescence had influenced the ultimate state of the affected leg or legs. A few patients were treated by conservative measures alone, most were subjected to some form of vein interruption, and a smaller number to anticoagulant therapy. Though many of these patients had suffered from pulmonary embolism, no attempt is made here to determine the relative life-saving value of the various procedures, the ultimate fate of the leg being the only consideration. Well developed obstructive thrombophlebitis is not included. I have previously discussed the late results of this disease.¹

Before describing the results obtained, I will name some of the considerations on which they seem to depend. The first is the influence of bed rest and the management of the return to normal activity upon the course of thrombosis and its effects, and in particular upon secondary edema and the establishment of a permanently competent collateral venous return.

The second is the significance of a damaged or intact superficial femoral vein. Common experience indicates that in the absence of thrombosis surgical interruption of the vein distal to the profunda leaves no permanent trace. But the Swedish School (Bauer², Zilliacus³, Birger⁴) maintains that thrombosis must be prevented from occupying the vein if serious aftereffects in the form of edema, induration and ultimate ulceration in the lower leg are to be avoided. One might expect therefore that the successful use of anticoagulants confining the process to the lower leg would give a different result from that of surgical interruption of the superficial femoral vein under similar circumstances.

The third consideration is the significance of the communications between the superficial and deep femoral veins and those of the combined deep and superficial femoral systems with higher veins. Here the recent anatomic observations of Edwards⁵ on the cadaver seem to me to be important. Edwards studied the connections in the lower and mid thigh between the superficial and profunda systems. In about 10 per cent of the thighs examined the two systems intercommunicated so freely as practically to be one. And in general the profunda veins offered themselves as useful collaterals when the superficial femoral was obstructed or rendered incompetent. By contrast the communications between the combined deep and superficial femoral vessels with the great circumflex veins of the upper thigh and the pelvic system above were found to be astonishingly few. Thus the collaterals available when the common femoral vein is interrupted proximal to the profunda are few and small.

A consideration to be kept in mind but which is only very incidentally taken up here, is the ultimate patency of the deep and superficial veins directly affected by thrombosis. It is assumed that any thrombus disables the valves of a vein whether or not obstruction is so complete that it permits a lumen to be restored only by canalization. It is further assumed that a canalized vein once valved but now valveless is more harmful to the individual than one which remains permanently obstructed since it can neither forward blood against gravity nor prevent excessive back pressure.

Material—No prophylactic interruptions are included. The fifty-five cases studied were private patients usually able and willing to make use of a planned convalescence. As a rule they had been attacked by thrombosis in everyday life rather than following operation or serious illness. In such persons one has a better opportunity to judge the extent of the thrombus before treatment is begun than in ill patients already confined to bed. Moreover the thrombosis of ambulatory life is far more often confined to one leg (as clearly appears here) so that one is able to compare the state of the affected limb with the second one. The first patient was treated nineteen years before this report, the last, six months before.

Treatment by Physiotherapy Only—Six legs were so treated all for thrombosis of the unilateral early type. Two suffered an early recurrence and were subjected to superficial femoral vein interruption. Of the other four three report themselves as well and one cannot be traced. These cases are of interest chiefly as showing that cures are often secured unpredictably by physiotherapy alone. The end results are similar to those of early disease treated by anti-coagulants.

SURGICAL INTERRUPTIONS AT VARIOUS LEVELS

Interruption of the Superficial Femoral Vein (Distal to the Profunda)—For the purposes of this study there have been 30 such interruptions on 29 patients*. These were the first operations undertaken. All but 2 patients have been seen personally or have given such a complete account of their present state that the observation can be trusted. Thrombosis was usually early and apparently confined to the lower part of the leg. In a few instances the disease was more advanced having passed the popliteal and invaded without fully obstructing the superficial femoral vein. In 1 the operation was followed by embolism for which heparin was successfully used. In only 2 instances were both legs involved (common femoral vein interruption was performed on one of these legs). A typical case and the first one treated is the following.

*Three other cases of superficial vein interruption are not included. They illustrate failure of the operation to prevent embolism and give no information as to the subsequent state of the leg. In one bilateral interruption for recurrent embolism was followed by embolism in a second unilateral interruption for embolism. In the other two cases the patient died of embolism shortly after the operation. In one case the patient died of embolism shortly after the operation. In the other two cases the patient died of embolism shortly after the operation.

A S F a single woman 43 years of age, was seen Dec 3 1929. As a result of a minor accident she had suffered a "subperiosteal" fracture of the fifth metatarsal bone (left). Treatment at first was by rest in bed. On ambulation the left ankle and lower leg swelled. On two subsequent occasions there was complete relief of edema and lameness of the calf on bed rest with recurrence on getting about. Seven weeks after the accident the left superficial femoral vein was ligated in continuity and the popliteal vein was exposed but not opened or ligated. Blood flow here could diminish but no thrombus was demonstrated. Postoperative treatment included elevation of the foot of the patient's bed and exercise of the leg in bed. No walking was allowed for nine days. After hospitalization for eleven days, the patient gradually returned to active life wearing an elastic stocking, and suffering no disorder of any sort. A nineteen year follow up shows no edema, no venous tasis, no lameness. The state of the two legs is identical.

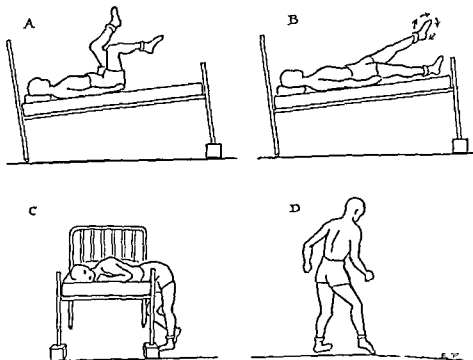


Fig 1—A and B. Cycle and foot exercises in bed. C. Preliminary walking with limited bed weight bearing and lower leg hydrotatic pressures. D. Full use of the lower leg muscle in walking.

Postoperative management of subsequent femoral vein interruption has followed a similar scheme and has included (1) rest in bed elevated four inches at the foot until all evidences of thrombosis have disappeared usually for about a week (2) bathroom privileges which seem to offer sufficient early ambulation (3) free exercise of the legs in bed including bicycle movements in the elevated position (4) light handling from toes to knees whenever the patient gets out of bed (5) walking exercise without weight bearing as shown in Fig 1 (6) for gradually increasing periods followed by resumption of normal

ambulation if no swelling or lameness is excited (6) bandaging or the wearing of an elastic stocking for the first few weeks after hospitalization in the more serious cases and as an optional matter for the early ones and (7) as a parallel precaution as the convalescence continues elevation of the legs above the body for brief periods during the day, to pay for periods of dependency. The plan has been to keep the venous pressure low, and especially to prevent wide variations. Obviously not all patients will pay equal attention to this system. One athletic muscular, youngish man began playing golf within one month of the operation, and now ten years later after a strenuous life during the late war shows no sign of circulatory disorder. (The thrombosis had caused recurring edema and cyanosis of the lower leg for several weeks before operation.)

Reports have been secured upon 28 of the 30 limbs treated by superficial femoral vein interruption. The results in 21 are excellent and these include 3 combined saphenous vein interruptions. In 5 others there is slight residual edema without complaints. In 2 others, previously existing varicose veins have recurred and progressed. Of the 2 untraced 1 had presented a perfect result at five months the second had stood for twelve hours a day from the start, and showed persistent edema with early skin changes a year later.

Evidently superficial femoral vein interruption for thrombosis confined to the lower leg is not very harmful to the venous return. That it throws the superficial femoral with its useful valves out of function is not proved but in any case experience with its use tends to lessen the validity of the Swedish contention. Following the interruption, a carefully controlled convalescence would seem to be unnecessary were it not for the occasional unpleasant post operative reaction in the lower leg to any sort of femoral vein section. For in one or two instances local pain muscular irritability and lameness have occurred on the first attempts to walk and have persisted until relieved by several days of elevation of the leg in bed and a second start. This has seemed to me to indicate a rather inflammatory type of thrombosis and extension into new vessels that is a failure of healing of the thrombotic process or even an actual spread with a threat to the collateral circulation. The use of anticoagulants following the interruption should prevent any such extension, including involvement of the profunda system and embolism from that source.

Common Femoral Vein Interruption—I have performed few of these operations and since they are most often used to combat embolism and relatively advanced thrombosis unilateral interruptions are a rarity. They tend to result probably by reason of the unsatisfactory connections of the combined superficial and deep femoral systems with higher veins in chronic edema venous engorgement and postphlebotic induration and ulceration. However they offer an opportunity for demonstrating that a carefully controlled convalescence can do much to secure a satisfactory leg. Typical bad and good results respectively, are illustrated by the following two cases.

A 32-year old unmarried woman a cook had noticed for three years light intermittent pain and swelling of the lower left leg. Lameness had been aggravated for one month

Examination revealed tight full posterior calf muscles and tenderness over the superficial femoral vein above the knee. At operation I had planned to interrupt the superficial femoral vein, but evidently (from the operative description) mistook the lower circumflex vein for the profunda sectioning the common femoral. No thrombus was found. After a normal convalescence for several weeks early return to work led to a recurrence of lameness and swelling. In spite of the use of an elastic stocking postphlebitic induration and ulceration developed within two and one-half years.

The second case was that of a 37-year-old married woman whom I had examined one year earlier because of incipient varicocity of the left saphenous vein. Some six months later she became pregnant for the first time and was subsequently subjected to a cesarean section. Nine days post partum thrombosis was evident in the dilated saphenous vein of the left thigh and irritability of the calf muscles indicated an underlying deep thrombosis. At operation a fresh soft clot was found to occupy the saphenous stump but nothing could be sucked out of the common femoral. High division was made of the saphenous vein with all entering branches and ligation of the common femoral just proximal to the profunda. The immediate effect was alarming. Before the leg could be elevated on the operating table it became blue and tense. The pulse rate rapidly increased and shock seemed imminent. However, on elevation of the legs to 30 degrees and saline venoclysis, the early signs of shock disappeared. The routine already outlined was then used. For the next three months the patient slept in a bed elevated four inches at the foot and undertook to see that the banished leg was given an opportunity to empty its veins by gravity whenever it had been obliged to do much standing in caring for her baby. I have never known anyone to behave so intelligently. As a result four years later after starting with an engorged edematous leg a blocked saphenous system and ligated common femoral she now uses no bandage or trasking notices only a trifling swelling of the ankle after an especially long day on her feet and has no postphlebotic sequelae. The patient is now again pregnant. At six months there is no edema, no cyanosis, but an increase of varicosity in the saphenous system is noted.

From my experience of only four well-controlled observations upon unilateral common femoral vein interruption I have received the impression that an immediate postoperative thrombotic reaction marked by swelling and lameness in the calf is more likely to follow common femoral vein interruption than any other procedure. As a late result edema and venous congestion are not

of femoral vein interruption at the Massachusetts General Hospital (1937 to 1946) made no distinction between the two procedures. He stated in effect that any subsequent edema is directly proportional to the extent of the thrombosis at the time of operation. This of course must be true only in a very general way and leaves out of consideration variations in the connections of the combined femoral systems with the veins above. I suggest that since Facer and Casper⁷ have shown how very often no valve is present in the common femoral or external iliac vein the profunda is quite capable of forwarding blood against gravity so long as the common femoral even though freshly thrombosed is not fully obstructed. It certainly cannot so act if the common femoral is ligated especially since its connections with the circumflex veins are so few and small. And I find it hard to believe that the great saphenous even though not itself

thrombosed or ligated, can carry much of the load. Indeed my experiences of combined saphenous and femoral vein interruption have caused me to feel that the usefulness of the saphenous as a collateral has been exaggerated.

Of the four cases of common femoral vein interruption one has an excellent result, one shows slight edema only, and the other two serious edema, postphlebitic induration and ulceration. Discussion of the results in these few instances will be included in the general discussion.

Common Iliac Vein Interruption—I¹⁸ have reported before upon the use of this operation in cases of thrombotic disease in which a lower ligation has seemed likely to be ineffective in controlling embolism and especially when an advanced thrombosis has seemed to call for the best sort of collateral venous return. In verification has shown that the end result has depended most accurately on the extent of the thrombosis at the time of the operation. I have reports covering five to eight years on six patients whom I am satisfied that the preoperative extent of the thrombosis was recognizable. In all repeated pulmonary embolism was the occasion of the operation.

In four cases the extent of thrombosis was believed to be slight though repeated embolism had occurred. In these the end result was excellent.

In one both saphenous and superficial femoral veins were known to be involved. The end result was slight enlargement of the lower leg and ankle with edema only on long standing. There were no skin changes.

In another thrombosis was advanced and the leg, blue to mid thigh. Chronic swelling resulted in both these advanced cases and in one of the two, postphlebitic induration and dermatitis.

Anticoagulant Therapy—I have only ten patients accurately paralleling those treated by vein interruption but their thromboses run all the way from the mild early sort to advanced high femoral nearly obstructive disease, attended by pulmonary embolism. The mild cases did well under the usual graded convalescence perhaps no better than patients treated by superficial femoral vein interruption though it has seemed to me that the legs returned more rapidly to normal. But it is in the advanced disease marked by high femoral vein involvement that the good results of combined chemotherapy and physiotherapy seem especially to stand out. Three of the ten were of this sort, of which one was bilateral and persistent. One only will be described.

A 40 year old man had been subjected to an appendectomy and two days after going home apparently well had suffered a serious pulmonary embolism. On returning to the hospital the right calf for the first time showed enlargement. Two days later I found the lower right leg considerably swollen with sufficient cyanosis to indicate a high femoral involvement. Operative surgery would probably have resulted in a bilateral common femoral interruption.

Although resistant to Dicumarol the patient's prothrombin percentage was finally brought down to 20 and maintained at about that level for one week. Banlaging, elevation of the foot of the bed and graduated exercises were employed. The patient was encouraged to continue gravity drainage and banlaging during the following year at the end of which time only slight enlargement of the superficial veins below the knee without

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SUMMARY

Experience with cases of early quiet thrombosis (phlebothrombosis) treated by vein interruption or by anticoagulation indicates that

1 The consistent use of gravity drainage, graded exercises, bandaging and the proper balance between dependency and elevation is of advantage in establishing a permanently efficient collateral venous return from the lower limbs and is especially required after an extensive thrombosis

2 The connections of the deep (profundi) with the superficial femoral vein are usually intimate and occasionally the two systems are practically one but the combined systems have unsatisfactory collateral connections with higher veins

3 The normal deep femoral system of veins may be expected to offer a good collateral pathway as long as the common femoral vein is open whether or not the common femoral has been invaded by thrombosis

4 Surgical obstruction of the common femoral vein necessarily and seriously opposes the establishment of an effective collateral circulation but may be compensated for by especially prolonged physiotherapeutic measures during the immediate and remote convalescence

REFERENCES

- 1 Homan J The Late Results of Femoral Thrombophlebitis and Their Treatment
New England J Med 235 249-53 1946
- 2 Bauer C the Sequels of Thrombosis Acta
chir
Zillion H : and Pulmonary Embolism With
Anti I Post Thrombotic Sequelae Acta
med
- 4 Burger I in the Lower Extremities Acta
chir
- 5 Flawls E A Applied Anatomy of the Femoral Vein and Its Tributaries Surg
Gynec & Obst 85 547-557 1947
- 6 Donaldson C A The Therapy and Prophylaxis of Venous Thrombosis and Pulmonary
Embolism S Clin North America 27 1037-1051 1947
- 7 Fair S A and Cooper S L Etiology of Varicose Veins From Anatomic Aspect
Based on Dissection of 38 Adult Cadaver J A M A 123 148 144
- 8 Homan J Deep Quiet Venous Thrombosis in the Lower Limb Preferred Levels
for Interruption of Vein Iliac Section or Ligation Surg Gynec & Obst 79
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edema remained. From the moment anticoagulation was employed the state of the leg rapidly improved and there was none of the reaction so often seen in this sort of case after common femoral vein section.

Among the seven early cases the end result in six is excellent. The seventh is an instance of recurrence after a bout of heparin with secondary treatment by Dicumarol. The immediate result was satisfactory, but the patient cannot be traced. Of the three advanced cases, one is described here as having an excellent result. The other two patients suffered from persistent high thromboses just short of obstructive thrombophlebitis. Both present as a late result slightly swollen limbs without cutaneous changes.

DISCUSSION

This report argues for treatment of venous thrombosis by anticoagulation with preservation of the common femoral pathway plus a carefully controlled scheme of physiotherapy. Blockage of the common femoral vein that is the outlet for both the deep femoral (profunda) vein and the superficial femoral rather than disablement of the superficial femoral alone would seem to represent what the Swedish school regards as a cause of permanent edema and its consequences. Superficial femoral vein section is a relatively harmless interruption but since it offers insecure protection against embolism (once thrombosis has started) it must if used be supported by anticoagulation.

Those who include in the aftertreatment of their cases of thrombosis no other directions than early and persistent ambulation go only halfway. Certainly walking is better than standing or sitting, but one cannot walk always and the newly used and presumably delicate and dilatable collateral pathways should not be overworked from the start. I recommend especially walking with the diminished hydrostatic venous pressure and weight bearing shown among the exercises in Fig 1*. A few minutes of this exercise can be carried out many times a day alternating with bed rest. Dr Warren has shown me his figures for the pressure lowering effect of walking as compared with standing and sitting. He points out what others of course have recorded that the resting erect venous pressure is the hydrostatic pressure of the column of venous blood from the point at which the needle is inserted in the vein to the level of the right auricle plus about 10 cm of strictly venous pressure. On walking this pressure is lessened by almost 50 per cent. At the same time lifting or straining tends to increase normal pressures both in the erect position and during exercise. Mere foot exercises in the sitting position cause no such a fall of pressure as actual walking. Bandaging the legs seems to me additional security against recanalization of the lower limb veins. Indeed the aim I am sure of

influence of use

* Dr Richard Warren was kind enough to prepare this illustration for me. Admin. train. in hispital in W. t. Ro bury

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REFERENCES

- 1 Homan J The Late Results of Femoral Thrombophlebitis and Their Treatment New England J Med 235 249-253 1946
- 2 Bauer C A Roentgenological and Clinical Study of the Sequela of Thrombosis Acta chir Scandinav 86 (Supp) 74 1942
- 3 Zilliacus H On The Specific Treatment of Thrombosis and Pulmonary Embolism With Anticoagulant With Particular Reference to the Post-Thrombotic Sequelae Acta med Scandinav supp 171 pp 1-21 1946
- 4 Jirger I The Chronic (Second) Stage of Thrombosis in the Lower Extremities Acta chir Scandinav 95 (Supp) 1-29, 1947
- 5 Flannery F A Applied Anatomy of the Femoral Vein and Its Tributaries Surg Gynec & Obst 85 547-557 1947
- 6 Donaldson C A The Therapy and Prophylaxis of Venous Thrombosis and Pulmonary Embolism S Clin North America 27 1037-1051 1947
- 7 Fagar S A and Casper S I Etiology of Varicose Veins From Anatomic Aspect Based on Dissection of 29 Adult Cadavers J A M A 123 149 1947
- 8 Homan J Deep Quiet Venous Thrombosis in the Lower Limb Preferred Levels for Interruption of Vein Iliac Section or Ligation Surg Gynec & Obst 79 70-82 1944

PHLEGMASIA CERULEA DOLENS AND GANGRENE ASSOCIATED WITH THROMBOPHLEBITIS

CASE REPORTS AND REVIEW OF THE LITERATURE

MICHAEL DEBAKEY M.D.* AND ALTON OCHSNER M.D., NEW ORLEANS, LA

(From the Departments of Surgery Tulane University of Louisiana and the Ochsner Clinic)

VASOSPASM in association with thrombophlebitis has been demonstrated both clinically and experimentally and is now generally recognized as a common accompaniment of that condition. However the occurrence in venous thrombosis of the extremities of clinical manifestations of arterial involvement which are so severe as to simulate acute arterial occlusion and which even terminate in gangrene is extremely uncommon. A review of the recent medical literature reveals 56 cases of this type, in 24 of which gangrene developed. Only 3 reports^{1, 2, 3} concerned particularly with this form of the disease appear in the American literature, most of the others having been recorded by French observers.

The extreme infrequency of this condition and the few reports on the subject in the American literature prompt the report of the following two cases which represent the two different types of the disease. In addition there are certain interesting features concerned with the pathogenesis of this unusual form of venous thrombosis which deserve further consideration.

REPORT OF CASES

CASE 1—A 22-year-old white man who had had ulcerative colitis for twelve years had been treated conservatively with good results until shortly before he was admitted to Touro Infirmary Jan. 10, 1944. Surgical therapy was then decided upon because the clinical manifestations of diarrhea, tenesmus and bloody stools could no longer be controlled by medical measures. At this time the patient's general condition was poor. He appeared chronically ill, dehydrated and undernourished and he had apparently lost considerable weight. Results of the physical examination were otherwise negative. The temperature ranged between 101 and 103° F. and the pulse between 100 and 110 beats a minute. The blood pressure was 112 systolic and 69 diastolic.

Results of laboratory investigations were negative in leukocyte and bacteriologic examinations except as follows: Blood hemoglobin 43.5 per cent, 69 Gm. per cent; red blood cells 5,500,000 per cubic millimeter; white blood cells 8,300 per cubic millimeter; neutrophils 81 per cent; platelets 400,000. The patient was reported to have severe secondary hypochromic anemia. Coagulation time was 1½ minutes. Bleeding time 1 minute and serum proteins 5.2 Gm. per cent.

On Jan. 17, 1944, the patient experienced a sudden severe pain in the left leg in the region of Scarpa's triangle. It came on both abruptly and violently and was only partially relieved by morphine. Almost immediately after the onset of pain the limb became numb and cold and began to assume a bluish-red color. Within one and one-half hours of normal coloration had been replaced by an intense cyanotic or dusky discoloration. Slight ecchymoses and areas of petechial hemorrhage were observed in the skin over the upper thigh particularly in the region of Scarpa's triangle (Fig. 1). Within one-half hour after the onset of pain the extremity began to swell and within the next hour it became greatly

*Read at the 34th annual meeting of the Society for Vascular Surgery, Chicago, Ill., June 6, 1945.
Now at the Department of Surgery Baylor University College of Medicine, Houston, Texas.

Fig 1



Fig 3

Fig 1 (Case 1) —Photograph of lower extremities taken shortly after operation showing edema of left leg particularly in thigh with intense cyanotic violaceous discoloration of skin

Fig 3 (Case 2) —Photograph of lower extremities taken on Feb. 7, 1947 shortly after admission of patient to hospital showing extensive swelling of both lower extremities with intense cyanotic violaceous discoloration of the skin. Purpuric area, petechial like lesion and some blisters and bullae may be observed over the dorsum of the foot and leg on the left side and early gangrenous change of the toes and distal portion of the foot are apparent on the right side

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The extreme infrequency of this condition and the few reports on the subject in the American literature prompt the report of the following two cases which represent the two different types of the disease. In addition there are certain interesting features concerned with the pathogenesis of this unusual form of venous thrombosis which deserve further consideration.

REPORT OF CASES

CASE 1—A 2-year-old white man who had had ulcerative colitis for twelve years had been treated conservatively with good results until shortly before he was admitted to Touro Infirmary Jan. 10, 1941. Surgical therapy was then decided upon because the clinical manifestations of diarrhea, tenesmus and bloody stools could no longer be controlled by medical measures. At this time the patient's general condition was poor. He appeared chronically ill, dehydrated and undernourished and he had apparently lost considerable weight. Results of the physical examination were otherwise negative. The temperature ranged between 101 and 103° F. and the pulse between 100 and 120 beats a minute. The blood pressure was 110 systolic and 60 diastolic.

Results of laboratory investigations were negative including fecal and urinary examinations except as follows: Blood hemoglobin 47.5 per cent, 0.8 Gm. per cent red blood cells—500,000 per cubic millimeter, white blood cells 8,000 per cubic millimeter, neutrophils 81 per cent, platelets 60,000. The patient was reported to have severe secondary hypochromic anemia. Coagulation time was 1½ minutes, bleeding time 1 minute and serum proteins 5.2 Gm. per cent.

When severe pain in the left leg in the calf and distally and was only partially relieved by morphine, the limb was amputated one and one-half hours after the onset of pain. The coloration had been replaced by an intense cyanotic violaceous discoloration. Slight erythema and areas of petechial hemorrhage were observed in the skin over the upper thigh particularly in the region of Scarpa's triangle (Fig. 1). Within one-half hour after the onset of pain the extremity began to swell and within the next hour it became extremely

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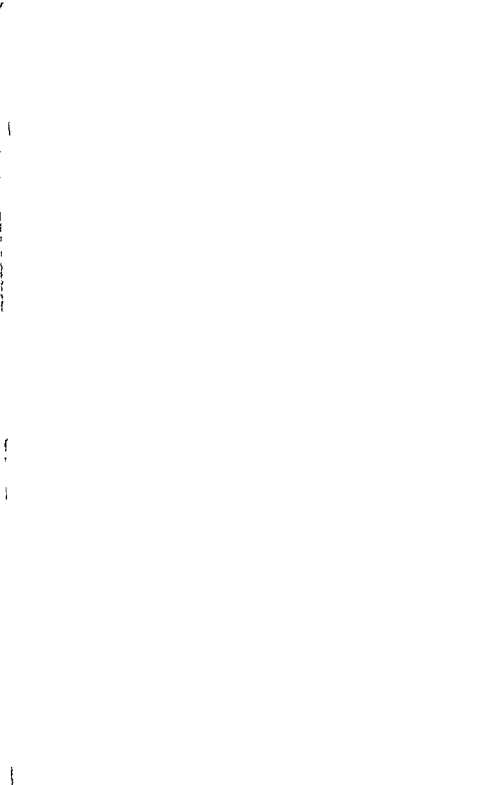
Fig 1



Fig 3

Fig 1 (Case 11)—Photograph of lower extremities taken shortly after operation showing extent of left leg particularly in thigh with intense cyanotic violaceous discoloration of skin.

Fig 3 (Case 7)—Photograph of lower extremities taken on Feb 5 1947 shortly after admission of patient to hospital showing extensive swelling of both lower extremities with intense cyanotic violaceous discoloration of the skin. Purpuric areas petechial like lesions and some blisters and bullae may be observed over the dorsum of the foot and leg on the left side and early gangrenous changes of the toes and distal portion of the foot are apparent on the right side.



swollen. Pulsations could be felt in the femoral artery and feeble pulsations could be felt in the posterior tibial and dorsalis pedis arteries when the patient was examined shortly after the onset. At the end of two hours however no arterial pulsations could be felt in the foot. Along with these changes in the limb, deterioration of the general condition occurred, which suggested circulatory collapse.

Pain was somewhat relieved by left lumbar sympathetic block with a 1 per cent solution of procaine hydrochloride but the color of the leg did not change. Because of the manifestations of impending shock the patient was given transfusions of whole blood and plasma.



Fig. (Case 1).—Photograph of lower extremities taken approximately fifteen months after thrombotic episode showing left leg completely recovered.

Another physician who saw the patient at this time (about one and one half hours after the onset) made a diagnosis of phlebotrombosis of the pseudoembolic type and undertook surgical exploration of the femoral vein under spinal anesthesia. A longitudinal incision was made beginning just above the inguinal crease and just medial to the femoral pulsation and was extended downward for a distance of about 15 cm. There was considerable edema of all the tissues. After the superficial and deep fascia had been divided the common femoral, superficial femoral, deep femoral (profunda) and saphenous veins were identified and freed. Coarse ligatures were placed loosely around these veins to provide a ready means for later hemostasis. The common femoral vein was greatly engorged but rather soft. The internal saphenous vein was also firm and full. The femoral artery was pulsating but was distinctly contracted. When the superficial femoral vein was opened granular clotted blood (of the "currant jelly" type) began to ooze from it when the incision was enlarged still more clots escaped. A large clot was finally sucked out of the distal end of the vein and another from the proximal end. Removal of these clots was followed by free bleeding. The vein was ligated both above and below the incision and the wound was closed in layers.

Immediately following the operation there was definite improvement in the patient's condition. Pain was greatly relieved. The extremity began to feel warmer, discoloration was less intense, and pulsations in the foot returned. Improvement was gradual but by the end of a week edema had completely subsided and by the end of two weeks discoloration had disappeared.

Ileostomy and appendectomy were performed Feb. 25, 1947. Recovery was uneventful and when the patient left the hospital on March 14 his general condition was much improved. The only significant finding in the extremities was a slight cyanotic tinge in the left foot and toes on dependency. An elastic bandage was advised.

When the patient was again examined Nov. 3, 1947, approximately nine months after the thrombotic episode, his general condition had continued to improve. There was no edema of the left extremity and no functional disturbances were apparent. The only departure from normal was a slight discoloration of the toes on dependency together with slight contraction of the toes.

The patient was last seen in May, 1948, when he returned for resection of the colon which was followed by an uneventful convalescence. At this time approximately fifteen months after the onset of the thrombosis, examination of the extremities revealed no abnormalities of any kind and it was evident that complete recovery had occurred (Fig. 2).

CASE 2—A 40-year-old white woman was seen in consultation in a north Louisiana town on Feb. 2, 1947, for vascular disturbances involving both lower extremities. She had begun to suffer from vague generalized abdominal pain, chiefly on the right side, on Jan. 21, 1947, and had been hospitalized forty-eight hours later after melena had appeared. For the next three days both pain and melena increased in severity. The blood which seemed to come from the large bowel was dark and mixed with foul material. Results of physical examination at this time were negative except for some tenderness on the right side, particularly in the lower quadrant. Urinalysis, blood culture, fecal examination and culture and roentgenograms of both the cecum and the abdominal men were essentially negative. The red blood cell count was 3,400,000 per cubic millimeter and the hemoglobin 40 per cent. The white blood count was 10,000 per cubic millimeter and the polymorphonuclear leukocyte percentage was 80.

On the fourth day of hospitalization after rectal bleeding had become less, a barium enema examination showed a definite rather extensive filling defect in the cecal region and ascending colon just below the hepatic flexure, whether it was of malignant or of inflammatory origin could not be determined. For the next day or two pain and tenderness were more definitely localized in the right lower quadrant and it was thought that a mass was developing in this area.

On January 25, the eighth day of illness, edema was observed in the right lower extremity. Within forty-eight hours the edema became massive in extent involving the whole extremity and presenting the appearance of phlegmasia alba dolens. The following day a similar condition developed on the left side. On the same day a left violaceous discoloration with purpura was apparent over the toes and dorsum of the right foot.

Although lumbar sympathectomy blocks were carried out on January 30 and 31 the areas of discoloration became larger and deeper colored and eventually presented a typical picture of early gangrene.

The administration of penicillin was begun as soon as the patient was admitted to the hospital but was discontinued at the end of seventy-two hours because of the appearance of a skin rash. The only other active therapy consisted of several transfusions of plasma and whole blood.

When the patient was first seen in consultation on Feb. 2, 1947, he appeared somewhat drowsy but perfectly rational and complained only of moderate discomfort in both lower extremities. The temperature at this time ran at between 100 and 101 F and the pulse rate was 100 to 110 per minute. Bowel sounds were limited to the abdomen and

lower extremities. Definite tenderness was elicited on the right side especially in the right lower quadrant and there was some rigidity in this area. An indeterminate mass was also palpable.

Both lower extremities were extensively swollen the left more than the right. On the left side the swelling was diffuse and pitting and involved the entire extremity. The edema was suggestive of phlegmasia alba dolens but the superficial veins were not as prominent as they usually are in that condition. The skin was pale and the temperature seemed slightly lower than normal. Pulsations in the dorsalis pedis, posterior tibial, and femoral arteries were not palpable but might have been obscured by swelling. Sensation was normal. There was considerable tenderness in the calf and on the medial aspect of the thigh.

On the right side swelling in the thigh had apparently subsided somewhat although the leg was still tensely swollen to the knee. A distinctive blackish discoloration suggestive of early dry gangrene was present over the toes and dorsum of the foot. It was more extensive on the outer than on the inner aspect. This discoloration as it extended upward to just below the knee gradually merged into a purplish deep red and then into a brighter red discoloration. Some large blebs or bullae were present over the dorsum of the foot and just above the ankle where swelling was particularly tense. Pulsations of the femoral artery were palpable but the dorsalis pedis and posterior tibial arteries could not be felt. Sensation was normal to the mid-dorsum of the foot then it gradually diminished and finally disappeared entirely in the apparently gangrenous area. Tenderness on the right side was limited to the calf. Motion although present was much diminished.

After the initial examination the abdominal lesion because of the manifestations of peritoneal irritation and the multiple locations in the cecum and ascending colon was thought to be inflammatory rather than malignant though malignancy naturally could not be excluded until the abdomen was opened. This lesion it was thought had precipitated a severe thrombophlebitis probably of the iliofemoral region with later extension to the iliac vein on the right and still later involvement of these vessels on the left. It was further postulated that severe arteriosclerosis had affected the lower leg and foot and that this factor superimposed upon the massive thrombosis had resulted in arterial thrombosis in the lower vascular channels and accounted for the development of gangrene in these areas. The concept of arteriosclerosis was supported by the fact that on the left side the extremity was pale and colder than normal and seemed to show rather poor filling of the superficial veins. On the right side vasospasm and thrombosis seemed a more reasonable explanation of the *pallor cordatus* than arterial embolism because pulsations were present in the femoral artery and the circulation in the thigh seemed normal.

Anticoagulants were not regarded as indicated because of the presence of an active bleeding lesion. The therapy administered consisted of transfusion, the red blood cell count now being 3,000,000 per cubic millimeter and the hemoglobin 60 per cent continued daily lumbar sympathetic blocks to maintain the lower extremities in a position at or slightly below heart level, protection of the extremities from the weight of the bed covering and other trauma, and the use of all possible measures to prevent infection. It was thought that amputation of the right leg would eventually be necessary after demarcation had occurred. It was also thought that abdominal exploration would be necessary to determine the character of the cecal lesion and its appropriate treatment.

On February 3 the day after the examination recorded discoloration similar to that present on the right side appeared in the left foot and on the following day the patient was removed to New Orleans by ambulance. On the way to the city she experienced for the first time a sharp pain in the right chest. Examination on arrival was substantially the same as when she had been seen forty-eight hours earlier except for the discoloration in the left foot and leg and the fact that edema of the lower extremities now extended symmetrically to the level of the umbilicus where it was rather sharply demarcated from normal tissues (Fig. 3).

All the laboratory examinations originally performed were repeated with the same negative findings. The red blood cell count was now 3,700,000 and the white count 24,500 per cubic millimeter. The hemoglobin was 10.1 Gm. per cent the hematocrit 33, and the

Immediately following the operation there was definite improvement in the patient's condition. Pain was greatly relieved. The extremity began to feel warmer, discoloration was less intense and pulsations in the foot returned. Improvement was gradual but by the end of a week edema had completely subsided and by the end of two weeks discoloration had disappeared.

Ileostomy and appendectomy were performed Feb. 20, 1947. Recovery was uneventful and when the patient left the hospital on March 14 his general condition was much improved. The only significant finding in the extremities was a slight cyanotic tinge in the left foot and toes on dependency. An elastic bandage was advised.

When the patient was again examined Nov. 2, 1947, approximately nine months after the thrombotic episode, his general condition had continued to improve. There was no edema of the left extremity and no functional disturbances were apparent. The only departure from normal was a slight discoloration of the toes on dependency together with slight contraction of the toes.

The patient was last seen in May 1948 when he returned for resection of the colon which was followed by an uneventful convalescence. At this time approximately fifteen months after the onset of the thrombotic examination of the extremities revealed no abnormalities of any kind and it was evident that complete recovery had occurred (Fig. 2).

CASE 2—A 40-year-old white woman was seen in consultation in a north Louisiana town on Feb. 2, 1947, for vascular disturbances involving both lower extremities. She had begun to suffer from vague generalized abdominal pain chiefly on the right side on Jan. 21, 1947, and had been hospitalized forty-eight hours later after melena had appeared. For the next three days both pain and melena increased in severity. The blood which seemed to come from the large bowel was dark and mixed with foul material. Results of physical examination at this time were negative except for some tenderness on the right side particularly in the lower quadrant. Urinalysis, blood culture, fecal examination and culture and roentgenogram of both the chest and the abdomen were essentially negative. The red blood cell count was 5,400,000 per cubic millimeter and the hemoglobin 40 per cent. The white blood count was 10,000 per cubic millimeter and the polymorphonuclear leucocyte percentage was 40.

On the fourth day of hospitalization after rectal bleeding had become less, a barium enema examination showed a definite rather extensive filling defect in the cecal region and ascending colon just below the hepatic flexure, whether it was of malignant or of inflammatory origin could not be determined. For the next day or two pain and tenderness were more definitely localized in the right lower quadrant and it was thought that a mass was developing in this area.

On January 29, the eighth day of illness, edema was observed in the right lower extremity. Within forty-eight hours the edema became massive in extent involving the whole extremity and presenting the appearance of phlegmasia alba dolens. The following day a similar condition developed on the left side. On the same day a deep violaceous discoloration with purpuric areolae appeared over the toes and dorsum of the right foot.

Although lumbar sympathetic blocks were carried out on January 30 and 31, the areas of discoloration became larger and deeper coalesced and eventually presented a typical picture of early gangrene.

The administration of penicillin was begun as soon as the patient was admitted to the hospital but was discontinued at the end of seventy-two hours because of the appearance of a skin rash. The only other active therapy consisted of several transfusions of plasma and whole blood.

When the patient was first seen in consultation on Feb. 2, 1947, she appeared somewhat drowsy but perfectly rational and complained only of moderate discomfort in both lower extremities. The temperature at this time ranged between 100 and 101° F. and the pulse rate was 100 to 110 per minute. Positive findings were limited to the abdomen and

lower extremities. Definite tenderness was elicited on the right side especially in the right lower quadrant, and there was some rigidity in this area. An indeterminate mass was also palpable.

Both lower extremities were extensively swollen, the left more than the right. On the left side the swelling was diffuse and pitting and involved the entire extremity. The edema was suggestive of phlegmasia alba dolens but the superficial veins were not as prominent as they usually are in that condition. The skin was pale and the temperature seemed slightly lower than normal. Pulsations in the dorsalis pedis posterior tibial and femoral arteries were not palpable but might have been obscured by swelling. Sensation was normal. There was considerable tenderness in the calf and on the medial aspect of the thigh.

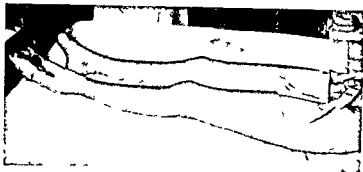
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All the laboratory examinations originally performed were repeated with the same negative findings. The red blood cell count was now 3,500,000 and the white count 14,500 per cubic millimeter. The hemoglobin was 10.1 Gm per cent, the hematocrit 33, and the



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C

Fig 4 (Case 3)—Therapeutic results of lower extremities of patient taken April 1, 1947 approximately three months after onset of condition. (A) The leg and foot appear pale and the cutaneous discoloration has disappeared and (B and C) the gangrenous areas in the toes and feet are well demarcated.

neutrophilic percentage 93. Sternal marrow studies revealed no significant findings. The platelet count was 93,700 per cubic millimeter, the bleeding time was 1 minute and coagulation time 3 minutes 15 seconds. The prothrombin time was 70 per cent of normal. Results of agglutination tests, blood chemical determinations, blood culture, and sputum examination were negative. Serum proteins were 5.75 Gm per cent (albumin 3.16 and globulin 2.59). Roentgenograms of the chest showed increased density in the right lower lobe and subsequent serial studies pointed more and more to the diagnosis of pulmonary infarction.

The patient gradually improved under a regimen of penicillin, transfusions and the usual supportive measure. The temperature which had been about 100 F. gradually fell and reached normal on Feb. 22, 1947. Abdominal pain and tenderness disappeared and the mass in the lower right side became only questionable palpable.

Edema of the abdomen and lower extremities slowly disappeared; the areas of gangrene began to demarcate and on February 13 the pulsations in the dorsalis pedis and posterior tibial vessels on both sides became palpable. Cyserologic examination on March 3 showed no abnormalities.



Fig. 5 (Case 2).—Photograph of lower extremities of patient taken on May 1, 1948, approximately sixteen months after onset of condition showing final result of reparative procedures on feet. The patient is able to walk with a good gait using specially made shoes.

Barium enema examination on March 1, showed the cecum contracted to a narrow tubular channel with the constricted segment sharply demarcated from the apparently normal bowel. A tentative diagnosis of ameboma was made despite the fact that results of proctoscopy examination and purgative tool studies were negative and emetine was given for ten days. At the end of this time another barium enema examination showed the same of aberrations as well as a fairly well visualized appendix. The diagnosis of appendicitis had not previously been entertained because of a history of appendectomy for acute appendicitis and the presence of a McBurney scar in the right lower quadrant.

The abdomen was explored on March 21 under spinal analgesia through a low para median incision. The cecum was bound down by relatively recent adhesions in which the appendix was included and from which it was freed with some difficulty. It was retrocecal and perforated at the base. At the site of perforation was a small well-walled off abscess. The appendix was removed and the defect in the cecum at the appendiceocecal junction was repaired. A small follicular cyst was removed from the right ovary. Exploration of the pelvic area showed a normal arterial tree. The iliac veins, however, were completely thrombosed on both sides and were represented only by fibrous cords up to their junction with the vena cava and as far distally as palpation was possible. The specimen excised for examination from the vein on the right was completely filled with a well-organized thrombus which on histologic examination showed some recanalization.

The postoperative course was satisfactory except for the development of a localized pericecal abscess which required drainage. The gangrenous areas on the lower extremities were permitted to become fully demarcated (Fig. 4) and on April 20 the large toe and the

second toe on the left foot and all the toes and part of the dorsum of the right foot were amputated. It was believed that the patient would have a functioning extremity on this side as well as on the left. Beginning May 3 1947, and in successive stages ending June 27 the defects on both feet were satisfactorily covered with skin graft. The patient was discharged from the hospital on Aug. 16 1947, on a regimen of gradually increasing exercises.

The patient returned for observation on Nov. 24, 1947. Her condition was found to be satisfactory. She had gradually begun to bear weight partially on the left foot with the aid of crutches and the use of specially made shoes. She had also continued to wear elastic bandages on both lower extremities. No edema had occurred.

The patient was again observed March 22 1948. At this time it was noted that sensation had advanced over the entire plantar surface of the flap on the right foot. Full weight bearing on both feet was begun after a special shoe was made for the right foot.

When she was last observed on May 21 1948 the patient was able to walk unaided with a good gait. She had continued to wear elastic bandages and there was no edema of the extremities. Only slight color changes were observed on dependency (Fig. 5).

CLINICAL PICTURE

The first of these crises is characteristic of the condition known as pseudo embolic phlebitis, the so-called blue phlebitis²¹ or phlegmasia cerulea dolens. Since 1929 when Trembleres and Veran first directed attention to it approximately 32 cases have been recorded in the literature.²² The condition is undoubtedly more frequent than these reports would suggest but it is still according to our experience an unusual form of venous thrombosis.

Most of the reported cases like our own follow a fairly consistent pattern. The clinical manifestations, all of which come on suddenly and progress rapidly, consist chiefly of pain, edema, discolorations and vascular impairment.

The pain which usually comes on with the greatest suddenness is excruciating and is often difficult to control with analgesics. It is located first in the calf or groin but eventually involves the whole limb.

Almost as striking as the violence of the pain is the discoloration of the limb which takes place immediately after the onset, sometimes within a matter of minutes, of petechial

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blebs and even bullae may appear. The cutaneous temperature of the involved extremity is likely to be diminished in comparison with the temperature of the normal side and during the early phase of the episode there is almost invariably diminution in cutaneous sensation as well as in motility.

Shortly after the onset pulsations in the arteries of the extremity become diminished and may disappear entirely. This observation together with the temperature changes, alterations in cutaneous sensation and loss of motility is strongly suggestive of arterial involvement and has led to exploration on the mistaken diagnosis of acute arterial occlusion or embolism.^{23 24 25 26 27 28}

Clinical manifestations of circulatory collapse often accompany or immediately follow the onset of the condition and are likely to be impressive. They include pale faces, weak pulse, tachycardia, and sometimes a lowering of the blood pressure. The patient is extremely anxious and has a sensation of impending death. These manifestations are probably related to the extent of the thrombosis, edema, and loss of fluids in the involved extremity. In the most severe cases the patient does die, never recovering from the initial state of circulatory collapse.

Most of the reported cases of blue phlebitis have occurred in the adult age group, from the third to the fifth decades, with both sexes affected about equally. The condition may involve any extremity but it has been observed most frequently in the left lower extremity. Among the 26 reported cases in which this information was recorded, 2 were in the upper (one on the right side and one on the left) and 24 were in the lower extremities, of which 7 were on the right side and 17 on the left. No particular circumstance seems to predispose to its development though some type of infection, including medical and surgical infections and puerperal sepsis, is often present. In an occasional case the condition has appeared after a relatively minor injury or in an apparently healthy individual. Of interest in this connection is the report of Bargen and Barker,⁷ who observed 5 cases of venous thrombosis in patients with ulcerative colitis, in 3 of which the manifestations closely resembled the form of blue phlebitis under discussion. It is noteworthy that although Bargen and Barker commented upon the frequency of venous thrombosis in ulcerative colitis, among the recorded cases of blue phlebitis those reported by these observers are the only ones, aside from our first case, with a background of ulcerative colitis.

The gravity of this form of venous thrombosis is shown by the fact that death occurred in 8 of the 32 cases recorded. In most of these cases death occurred shortly after the onset of the condition, the patient never recovering from the initial state of circulatory collapse. It is interesting that although 6 patients in the entire group showed manifestations of pulmonary infarction, only 1 of the 6 died.

The subsequent course of patients who recover from the initial episode is fairly characteristic of phlegmasia alba dolens or the more common form of iliofemoral thrombophlebitis, with gradual disappearance of cutaneous discoloration, progressive subsidence of edema, and return of normal arterial pulsations. In many of the recorded cases ultimate recovery was complete and there were few or no residual postphlebotic manifestations.

The second case which we are reporting represents an even more severe type of venous thrombosis in which actual gangrene of a part of the extremity occurs. One of the earliest instances of this kind was reported in 1932 by Bergeret (Guillaume and Delarue).⁸ To date, about 24 cases have been reported in the literature,⁹ the most recent by Haimovici and Suffness,¹⁰ in 1946. The age and sex distribution is similar to that observed in blue phlebitis. No preceding or associated illness seems characteristic, but most of the patients had

second toe on the left foot and all the toe and part of the dorsum of the right foot were amputated. It was felt that the patient would have a functioning extremity on this side as well as on the left. Beginning May 3, 1947 and in successive stages ending June 27, the defects on both feet were satisfactorily covered with skin graft. The patient was discharged from the hospital on Aug. 16, 1947 on a regimen of gradually increasing exercises.

The patient returned for observation on Nov. 24, 1947. Her condition was found to be satisfactory. She had gradually begun to bear weight partially on the left foot with the aid of crutches and the use of specially made shoe. She had also continued to wear elastic bandages on both lower extremities. No edema had occurred.

The patient was again observed March 2, 1948. At this time it was noted that enervation had advanced over the entire plantar surface of the flap on the right foot. Full weight bearing on both feet was begun after a special shoe was made for the right foot.

When she was last observed on May 21, 1948 the patient was able to walk unaided with a good gait. She had continued to wear elastic bandages and there was no edema of the extremities. Only slight color changes were observed on dependency (Fig. 3).

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The first of these cases is characteristic of the condition known as pseudo embolic phlebitis, the so-called blue phlebitis²¹ or phlegmasia cerulea dolens. Since 1929 when Tremolieres and Veran first directed attention to it approximately 32 cases have been recorded in the literature.²² The condition is undoubtedly more frequent than these reports would suggest, but it is still according to our experience an unusual form of venous thrombosis.

Most of the reported cases like our own follow a fairly consistent pattern. The clinical manifestations all of which come on suddenly and progress rapidly consist chiefly of pain, edema, discolorations and vascular impairment.

The pain which usually comes on with the greatest suddenness is excruciating and is often difficult to control with anodines. It is located first in the calf or groin but eventually involves the whole limb.

Almost as striking as the violence of the pain is the discoloration of the limb which takes place immediately after the onset, sometimes within a matter of minutes. The color is deeply violaceous or cyanotic and often purpuric areas of petechial like lesions are scattered over the extremity. Sometimes this dis-

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Shortly after the onset pulsations in the arteries of the extremity become diminished and may disappear entirely. This observation together with the temperature changes, alterations in cutaneous sensation and loss of motility, is strongly suggestive of arterial involvement and has led to exploration on the mistaken diagnosis of acute arterial occlusion or embolism.^{23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100}

If gangrene has occurred every effort should be made to control infection and permit the process to become demarcated. In the majority of instances the gangrene is of the dry type and the eventual loss of tissue is usually not as great as at first seems likely to occur. For this reason a conservative attitude should be taken toward amputation which should be postponed until the full extent of the eventual tissue loss has become apparent.

PATHOGENESIS

The form of venous thrombosis discussed in this communication is distinctly different from the ordinary varieties of phlebothrombosis and thrombophlebitis. The dramatic often violent onset the striking clinical picture and the severity of the manifestations bear little resemblance to the clinical manifestations of the other forms. Particularly impressive are the manifestations which apparently reflect involvement of the arterial tree. They are characteristic and are often so pronounced that as has already been mentioned they suggest the diagnosis of acute arterial occlusion and in some instances have actually led observers into surgical exploration of the arteries for the presumed occlusive process.

These various considerations naturally raise certain questions as to the pathogenesis of this type of venous thrombosis and as to the reasons for the difference between it and the more common milder forms. Since however the etiology of the more common types is still poorly understood, it is natural that no satisfactory explanation for the more infrequent and more severe form can be advanced. The violence of the onset as Magendie and Tinguet³ noted and the severity of the manifestations suggest that the phenomenon of intra-venous coagulations occurs suddenly with the 'brutality' of a physicochemical reaction. But what are the factors that precipitate such a reaction? And why are these factors whatever they may be operative in some cases and not in others? It is well known that in phlebothrombosis an extensive thrombotic process may be present when there are few local or systemic clinical manifestations or none at all. Even in phlegmasia alba dolens the classical form of thrombophlebitis thrombosis may be extensive whereas clinical manifestations develop only gradually. Why do these forms of thrombosis assume a less violent or actually mild character? Obviously in the severe form we are discussing some changes occur in the coagulative mechanism which lead to sudden and massive thrombosis. The nature and cause of the process however remain to be clarified.

Of particular interest in the pathogenesis of the severe form of venous thrombosis are the arterial manifestations and the occurrence of gangrene particularly its occurrence in the absence of organic lesions of the arterial tree. The absence of such lesions has been clearly demonstrated in many of the reported cases by careful studies including arteriography, complete dissection of amputated extremities, autopsy observations and extensive histologic examinations of the vessels. These studies have confirmed the absence of organic arterial lesions and have shown that thrombosis of the venous system is so extensive as to include even the smallest radicles.

had some type of infection, such as appendicitis peritonitis puerperal sepsis or pneumonia. One or two had suffered some injury of the extremity, and one had a malignant disease.

Whereas the onset and clinical manifestations in this group of cases may be similar to those of blue phlebitis in a few of the recorded cases as in our own, the onset was less dramatic and pain was less severe. In Gregoire's case the patient had only a moderate degree of pain in the foot and in the case reported by Bergeret, Guillaume and Defrue the clinical picture developed rather gradually. In other words the early course of the disease may take one of two possible forms. In the first it may suggest a typical thrombophlebitis or phlegmasia alba dolens with the subsequent development of fairly characteristic arterial manifestations. In the other the sequence of events is reversed characteristic arterial manifestations appear at the onset and the subsequent course of the disease may suggest phlegmasia alba dolens.

In all cases regardless of the character of the onset the violaceous discoloration of the affected limb becomes more intense until typical gangrene gradually appears usually in the toes and the distal portion of the foot. In some instances the gangrenous process may spread up the leg in others it becomes well demarcated. Any extremity may be involved but it seems to occur most frequently in the left lower extremity. Occasionally bilateral involvement has been observed as in our case.

The prognosis in cases of venous thrombosis associated with gangrene is not good. Death occurred in 11 of the 24 recorded cases and in all but 3 of the remainder a major amputation of the extremity was necessary. In those 3 cases as in our own only a portion of the foot and toes was lost.

Pulmonary infarction occurred in 2 of the 24 recorded cases, as it did in our second case and in an occasional instance was the first manifestation of the venous thrombosis.

THERAPY

Numerous therapeutic measures none of them strikingly successful have been employed in this form of venous thrombosis. Attempts to produce vaso-dilatation and counteract vasospasm have included the use of vasodilator drugs such as acetylcholine and papaverine and procaine hydrochloride block of the regional sympathetics or periarterial sympathectomy. In some cases dramatic improvement occurred but it was usually temporary except in a few instances in which recovery occurred without gangrene. Similar recoveries however have followed the use of other conservative measures.

Operative intervention consisting of exposure of the femoral vessels thrombectomy and periarterial sympathectomy has not been notably successful. On the other hand the striking results which followed thrombectomy and ligation in the first of the cases reported in this communication would seem to warrant this type of therapy. It would also seem indicated as a prophylactic measure to guard against pulmonary infarction and embolism which are not infrequent accompaniments of this condition. Lumbar sympathetic block with procaine to counteract vasospasm also seems indicated.

venous thrombosis associated with gangrene the primary factor responsible for the arterial manifestations is massive venous occlusion. Blockage of the venous return however, in addition to being practically complete, must take place suddenly to produce the results described. This may conceivably initiate an immediate and severe degree of vasospasm which as emphasized by some observers^{21 31 33 43 45} would tend to aggravate the ischemic process. These conditions as Fontaine, Israel and Pereira¹⁷ have pointed out are only occasionally met because of the richness and abundance of the collateral venous channels. Fortunately therefore the clinical condition is likely to be encountered only very infrequently.

SUMMARY

1 The occurrence in venous thrombosis of the extremities of clinical manifestations of arterial involvement which are so severe as to simulate acute arterial occlusion and which even terminate in gangrene is extremely uncommon. A review of the recent medical literature reveals only 56 cases of this condition.

2 Two cases representing the two different types of venous thrombosis (pseudomphobic phlebitis and venous thrombosis with actual gangrene of the extremity) are reported.

3 The clinical manifestations follow a consistent pattern. In both forms of the disease the condition is associated with rather striking clinical manifestations which develop suddenly and progress rapidly consisting chiefly of severe pain, edema, evanescent violaceous discoloration and evidence of arterial deficiency. The early course of the second form in which gangrene occurs may suggest a typical thrombophlebitis or phlegmasia alba dolens with the subsequent development of fairly characteristic arterial manifestations or the sequence of events may be reversed.

4 Both conservative measures such as the use of vasodilator drugs and procaine hydrochloride block of the regional sympathetics or periarterial sympathectomy and operative intervention consisting of exposure of the femoral vessels, thrombectomy and periarterial sympathectomy have been advocated. None has been strikingly successful.

5 The prognosis in both forms of the disease is grave.

6 Evidence is offered which suggests that sudden complete blockage of the circulation by venous thrombosis is the primary factor in the mechanism involved in this ischemic disturbance. Vasospasm is believed to play a secondary and contributory role in the pathogenesis of this condition.

REFERENCES

- 1 Allen F A, Barker N W, Hine F A Jr. Peripheral Vascular Disease Philadelphia 1946 W B Saunders Company.
- 2 Audier M. La symptomatologie arterielle des phlebitides de membres et de leurs sequelles. Progr med 1: 729-738 1925.
- 3 Audier M. Thrombose veineuse aigue simulant l'embole arterielle des membres. Progr med 26: 84-90 1916.
- 4 Audier M and Homoyet H. Les phlebitides des membres avec gangrene. Arch d mal du coeur 31: 91-916 1938.

Two factors spasm and massive venous obstruction, have been postulated as responsible for the striking arterial manifestations in the severe types of venous thrombosis. The role of vasospasm in their productions is difficult to evaluate. Some observers are inclined to regard it as important. Others doubt that it plays a significant part or indeed any part at all. There is strong evidence of arterial spasm in many of the reported cases. Its presence is suggested clinically by the diminution or absence of arterial pulsations and oscillations in the early state of the condition while their subsequent return to normal is associated with improvement in the condition of the limb. Other evidence of the presence of vasospasm lies in the contracted appearance of the artery at operation and the dramatic, though often temporary improvement in pulsations following sympathetic block or the administration of vasodilating agents. It has been demonstrated clinically and experimentally that vasospasm exists in thrombophlebitis and that this vasospastic action can be abolished by the interruption of the regional sympathetic pathways.^{12, 13} It has also been shown that this vasospasm in acute phlebitis involves the veins as well as the arteries and that it is probably responsible in great measure for the pain.¹⁴ The fact however that the severe type of venous thrombosis may continue to progress to actual gangrene in spite of vigorous antivasospastic measures and the transient improvement produced by them seems to indicate that vasospasm does not play a primary role in the genesis of this condition. It would seem in fact, that in the mechanism of its production some factor or factors other than vasospasm play the dominant role and that the role of vasospasm is merely temporary and contributory to the ischemic process.

The second and more plausible explanation of the mechanism involved in the ischemic disturbance is blockage of the circulation by venous thrombosis. What this amounts to is that although blood can enter the extremity through the patent arterial tree it cannot leave it because the venous circulation is obstructed by thrombosis. This interference with the circulation soon leads to stasis of the arterial blood flow, at least in the more terminal parts of the vascular bed with resulting ischemia anoxia of the tissues, and gangrene.

That such a mechanism is possible has been demonstrated experimentally. Fontaine and Pereira¹⁵ have shown that gangrene could be produced in animals only when there was complete blockage of the venous blood flow. We¹⁶ have also shown experimentally that a profound effect upon the peripheral pulse volume occurs when a significant increase in the venous pressure is produced by obstruction of the main venous outflow. In the following occlusion of the venous channel in these experiments the venous pressure was 19 times the normal value whereas the pulse volume was 51.5 per cent. It was possible that the volume of pulsations was probably of properties of the vessels caused in turn by

It is thus apparent that obstruction of the venous circulation provided that it is of sufficient extent can cause blood flow. On this basis it seems reasonable

venous thrombosis associated with gangrene the primary factor responsible for the arterial manifestations is massive venous occlusion. Blockage of the venous return however in addition to being practically complete must take place suddenly to produce the results described. This may conceivably initiate an immediate and severe degree of vasospasm which, as emphasized by some observers^{3, 21, 31, 32, 37, 45, 45} would tend to aggravate the ischemic process. These conditions as Fontaine, Israel and Percival¹⁷ have pointed out are only occasionally met because of the richness and abundance of the collateral venous channels. Fortunately therefore the clinical condition is likely to be encountered only very infrequently.

SUMMARY

1 The occurrence in venous thrombosis of the extremities, of clinical manifestations of arterial involvement which are so severe as to simulate acute arterial occlusion and which even terminate in gangrene is extremely uncommon. A review of the recent medical literature reveals only 56 cases of this condition.

2 Two cases representing the two different types of venous thrombosis (pseudocombolic phlebitis and venous thrombosis with actual gangrene of the extremity) are reported.

3 The clinical manifestations follow a consistent pattern. In both forms of the disease the condition is associated with rather striking clinical manifestations which develop suddenly and progress rapidly consisting chiefly of severe pain, edema, cyanotic violaceous discoloration and evidence of arterial deficiency. The early course of the second form in which gangrene occurs may suggest a typical thrombophlebitis or phlegmasia alba dolens with the subsequent development of fairly characteristic arterial manifestations or the sequence of events may be reversed.

4 Both conservative measures such as the use of vasodilator drugs and pneumatic hydrochloride block of the regional sympathetics or periaxillary sympathectomy and operative intervention consisting of exposure of the femoral vessels, thrombectomy and periaxillary sympathectomy have been advocated. None has been strikingly successful.

5 The prognosis in both forms of the disease is grave.

6 Evidence is offered which suggests that sudden complete blockage of the circulation by venous thrombosis is the primary factor in the mechanism involved in this ischemic disturbance. Vasospasm is believed to play a secondary and contributory role in the pathogenesis of this condition.

REFERENCES

- 1 Allen F A, Barker N W, Hine F A Jr. *Peripheral Vascular Disease*. Philadelphia 1940. W B Saunders Company.
- 2 Audier M. La symptomatologie artérielle des phlébites de membre et de leurs séquelles. *Progrès méd* 1: 29, 38, 39, 50.
- 3 Aubier M. Thrombose veineuse aiguë simulant l'embolie artérielle de membre. *Paris méd* 26: 384, 90, 39, 40.
- 4 Aubier M and Hamovici H. Les phlébites des membres avec gangrène. *Arch d mal du cœur* 31: 99, 90, 11, 5.

- 36 Pallin Gustaf The Differential Diagnosis, Arterial Embolism-venous Thrombosis Acta
chir Scandinav 65 553 563 1949
- 37 Panpani D Thrombophlebite acuta degli arti fenomeni pseudoembolici, Policlinico
(sez chir) 45 470 49, 1939
- 38 De Sousa Pereira A The Innervation of the Veins Its Role in Pain Venospasm,
and Collateral Circulation SURGERY 19 731 742 1946
- 39 Pringle J H Massive Ischemic Gangrene With Thrombosis of Veins and Patent
Arterie, Claspow M J 129 126 130 1934
- 40 Sackenreiter G Observations a propos de la ' phlegmatia cerulea dolens ' Presse
med 48 515 1940
- 41 Swartz W B Weeder S D and McLaughlin E F Thrombosis and Gangrene of
Right Arm Associated With Polycythemia Vera, Its Relation to ' Effort Throm-
bosis, Ann Surg 116 184 193 1942
- 42 Tilley J H Gangrene of the Extremities in Puerperal Thrombophlebitis Am J
Obst & Gynec 36 157 158 1928
- 43 Tremolieres F and Veran P Syndrome d'obliteration arterielle du membre inferieur
droit apparu au cours d'une phlebite superficielle et profonde avec embolies
pulmonaires effect therapeutique de l'acetylcholine Bull med, Paris 43 1101 1105
1949
- 44 Uggeri, C and Massone A La sintomatologia arteriale delle flebiti degli arti, Arch
ital di chir 49 470 479, 1934
- 45 Wertheimer, P and Frieh P " "
des membres documents chir
- 46 See references 7 10 11 15 17
- 47 See references 1 5 6 8 13 14

THE EARLY RESULTS OF SYMPATHECTOMY IN FAR ADVANCED ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE

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INDIVIDUALS suffering from the effects of obliterative arteriosclerosis of the peripheral vessels have long been thought to be beyond the reach of surgical aid by measures destined to improve the circulation. This conclusion is not compatible with our experiences or with the observations of other investigators who have performed lumbar sympathectomy on these patients. The belief that interruption of the autonomic nervous system pathways has little to offer these patients is not tenable if one reviews the numerous reports from vascular clinics of satisfactory results following sympathectomy for arteriosclerosis obliterans.¹⁻⁵

Subsequent to the report of White⁶ on the technique of blocking the lumbar sympathetics with procaine hydrochloride Hothorn,⁷ Reicher⁸ and Baker⁹ observed that blockade by chemical means of the lumbar sympathetic chain in peripheral arteriosclerotic vascular disease often produced unanticipated good results. Permanent interruption of the lumbar sympathetic chain by ganglionectomy has been performed by several investigators for obliterative sclerosis of the peripheral arteries. Ives¹ performed sympathectomy on seven patients in whom the outstanding symptom was intermittent claudication. The average age of his group was 60 years. Six of the results he classed as favorable. One patient obtained no relief. Harris² has reported thirteen lumbar sympathectomies in patients with advanced peripheral arteriosclerosis with 40 per cent good results. Atlas³ followed twelve cases for a period of at least twelve months; seven patients obtained relief from intermittent claudication; three were classified as improved while two were unimproved. He observed further that walking capacity was rarely immediately increased; many months often were necessary for maximum benefit. Trimble, Cheney and Moses⁴ observed benefits obtained in twenty-four sympathectomized individuals all having been followed for more than twelve months. Eight of these were classified as greatly improved, nine showed some improvement and four obtained no relief. Freeman and Montgomery⁵ reported six lumbar sympathectomies performed on individuals with intermittent claudication. They observed an increase in walking distance from one to fifteen blocks following this procedure. De Takats and co-workers¹⁰ reported twenty-five sympathectomies on individuals with peripheral arteriosclerosis. They divided their cases into four groups based upon the degree of claudication and severity of trophic changes. All of their cases were benefited to some degree by operation. They further

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concluded that (1) Extremities warm faster and cool slower on direct exposure after sympathectomy, (2) the high vasoconstrictor tonus in the sitting or standing position is abolished, (3) vascular exercises are more effective and (4) cross stimulation between sympathetic and demyelinated sensory fibers is abolished. Yeager and Cowley⁸ published the resultant effects of lumbar sympathectomy in 150 cases. Of this group they classified forty six (30.66 per cent) as improved. In fifty six patients amputations were necessary following sympathectomy. They observed however, that seventy three patients in this series did not have adequate preoperative vascular studies. The recent report of Freeman, Leads and Gaidner⁹ gave an excellent summary of the entire subject.

In 1945 we became interested in the possibilities of salvage, by lumbar sympathectomy, of extremities affected by far advanced arteriosclerotic peripheral vascular disease with associated ulceration and gangrene. This group had previously been doomed to ultimate amputation in a very high per cent of cases because of the advanced stage of their disease. It was felt that if any significant percentage of them could be rehabilitated following sympathectomy an important advance in the therapy of this heretofore rather hopeless group would have been achieved.

During the two and one half year period from July 1, 1945 to Jan. 1, 1948 there were 750 patients with arteriosclerotic peripheral vascular disease seen in the surgical outpatient department. Two hundred twenty of these were classed as Grade III or IV according to the classification proposed by de Takats and co-workers.¹ During this same period, 103 lumbar sympathectomies have been performed in 83 patients who had not previously been considered satisfactory candidates for this operation.

Certain patients however were not considered suitable subjects for sympathectomy because of far advanced cerebral and renal arteriosclerotic involvement. Furthermore it was felt that the operation was not indicated in patients with cardiac decompensation that could not be adequately controlled. Poor results were observed early in the series in patients with paradoxical response to paravertebral block that is those whose symptoms were aggravated or showed evidence of deleterious effect upon the remaining circulation and in patients presenting marked atrophy of the soft tissues with resultant skeletization. These patients were subsequently excluded from operative consideration.

Individuals selected for lumbar sympathectomy were considered suitable if they demonstrated (1) some response to sympathetic block, either subjective symptomatic relief or temperature rise in the involved extremity, (2) evidence of arrest or improvement of the process on a period of conservative therapy which included

- (a)
- (b)
- (c)

triethylaminonium chlo
ride¹¹ or paravertebral lumbar block.

- (d) Puerper Allen exercises
 (e) chemotherapy directed at control of whatever infection was present

(3) as a last resort in patients showing lack of response to conservative measures and in whom no specific contraindication existed

The operative approach utilized was a transverse flank incision with extraperitoneal dissection. Patients were made ambulatory the same afternoon of the day following operation and were discharged when the skin sutures were removed usually about the seventh day. Spinal anesthesia was preferred. Those patients presenting a moderately severe hypertension were given gas oxygen ether inhalation anesthesia.

This report will concern itself with the first 63 patients operated upon prior to July 1, 1947 inasmuch as these have been followed a sufficient period of time to allow a more critical evaluation.

Of this group 50 were men and 13 were women a ratio of 4:1 of men over women. The youngest patient was 32 years of age the arteriosclerotic process having been proved by pathologic examination. The oldest patient was 75 years. By far the greatest number of patients were in the sixth and seventh decades (51 to 70 years). Average age of this group was 58.2 years (Table I).

TABLE I. GENERAL STATUS ON ADMISSION OF PATIENTS WITH FAR ADVANCED ARTERIOSCLEROSIS OBITERANS WHO UNDERWENT LUMBAR SYMPATHETOMY

Number of patients	63
Sex of patients	
Males	50
Females	13
Ratio	4:1
Age (years)	
31 to 40	1
41 to 50	3
51 to 60	14
61 to 70	3
71 to 80	2
Youngest patient	32
Oldest patient	75
Average age	58.2
Extremity involvement	
Left lumbar sympathectomy	2
Right lumbar sympathectomy	23
Bilateral sympathectomy	11
One stage	9
Two stage	-
Duration of symptoms	
Less than 1 month	6
1 to 6 months	13
6 to 12 months	10
1 to 2 years	10
2 to 5 years	13
5 to 10 years	9

Seventy-four lumbar sympathectomies were done on the 63 patients. Of 11 bilateral operations 9 were done in one stage and 2 in two stages. A left lumbar sympathectomy was done in 27 patients and a right in 23; the incidence of involvement of the lower extremities being about equal.

TABLE II PRESENTING SYMPTOMS OF SIXTY THREE PATIENTS UNDERGOING LUMBAR SYMPATHECTOMY

SYMPTOMS	NUMBER	PER CENT
Pain in the extremity	59	93.6
Symptomatic cold feet	45	71.4
Intermittent claudication	31	49.2
Ulceration	40	63.5
Gangrene	40	63.5

Symptoms causing these patients to seek medical aid varied greatly in composition and number (Table II) Pain in the extremity was present in 59 cases (93.6 per cent) symptomatic cold feet 45 (71.4 per cent), intermittent claudication 31 (49.2 per cent) ulceration, 40 (63.5 per cent), and gangrene 40 (63.5 per cent)

Duration of symptoms prior to being seen at the University Hospital are shown in Table I Less than 50 per cent had the symptoms for shorter periods than one year Nine patients (14.3 per cent) had the onset of symptoms more than five years prior to their first visit at the hospital

Twenty one (33.3 per cent) patients had diabetes mellitus Only 4 were considered adequately controlled at the time of admission The remaining 17 were uncontrolled poorly controlled or undiagnosed when first seen Results of sympathectomy in this group will be presented in detail later

Some atrophy of the involved extremity was observed in 38 patients (60.3 per cent) The posterior tibial and dorsalis pedis pulses were absent in 53 cases The femoral pulse was absent in only 3 patients Nine cases presented a single palpable pedal pulse or questionably palpable pulses No record of pulses was obtainable in one case Infection sufficiently severe to necessitate administration of antibiotics was observed in 13 patients

Final grading³ of these patients was as follows Grade I 0 Grade II, 4, Grade III 12 Grade IV, 47

TABLE III RESPONSE OF PRESENTING SIGNS AND SYMPTOMS FOLLOWING LUMBAR SYMPATHECTOMY

SYMPTOMS	NUMBER	RELIEF, ARREST, OR IMPROVEMENT	PER CENT
Pain in the extremity	59	46	78.2
Symptomatic cold feet	45	32	71.1
Intermittent claudication	31	27	87.0
Ulceration	40	23	57.5
Gangrene	40	28	70.8

RESULTS OF OPERATION (TABLE III)

Pain (Table IV) —Fifty nine patients complained of pain in the involved leg, varying from minimal distress to constant disabling rest pain Of these

TABLE IV RESPONSE TO LUMBAR SYMPATHECTOMY OF PATIENTS WITH PAIN IN THE EXTREMITY DUE TO ARTERIAL INSUFFICIENCY

Patients with painful extremities	59
Constant rest pain	31
Total relief of pain	28
Partial relief of pain	19
No alleviation or subsequent amputation	12

28 (47.5 per cent) were completely relieved of pain following sympathectomy. Another 18 (30 per cent) patients obtained some alleviation of pain. The remainder obtained no help and all but 2 of these finally had amputations.

Cold Feet (Table V)—Of the 45 patients complaining of cold feet symptomatic relief was obtained in 32 cases (71.1 per cent). Two obtained no help, and the remainder without relief eventually had amputations.

TABLE V RESPONSE TO LUMBAR SYMPATHECTOMY OF SYMPTOMATIC COLD FEET

Number of patients	45
Symptomatic relief	32
Persistence of symptoms	2
Subsequent amputation	11

Intermittent Claudication (Table VI)—Of 31 cases with intermittent claudication, 27 (87.0 per cent) patients obtained some measure of improvement or arresting of symptoms. Six out of 7 with unilateral moderately severe claudication obtained relief. Of the group of 10 with unilateral severe claudication 9 were helped. The results were just as good with bilateral intermittent claudication. Both patients with moderately severe involvement obtained relief while 10 out of 12 with severe involvement obtained significant alleviation. The 4 patients who obtained no benefit eventually had amputations. It must be clearly understood that although some benefit was obtained in 87 per cent that no patient obtained unlimited walking distance from operation.

TABLE VI RESULTS OF SYMPATHECTOMY IN PATIENTS WITH INTERMITTENT CLAUDICATION

	CS	IMPROVED OR ARRESTED	PER CENT
		6	85.7
		1	90.0
		2	100.0
		10	83.3
		7	87.0

Ulceration (Table VII)—Forty patients presented ulcerations secondary to arteriosclerotic ischemia. There were multiple ulcerations in 7 cases, the largest number in any one case being 11. Thirty three in this group also had

TABLE VII RESPONSE TO LUMBAR SYMPATHECTOMY OF PATIENTS WITH ARTERIOSCLEROTIC ULCERATION

Patient with arteriosclerotic ulceration		40
Total sites involved		40
Toes	27	
Malleolus	7	
Foot	11	
Leg	2	
Previous amputation site	1	
Multiple ulcerations	7	
Largest number single case	11	
Associated gangrene	33	

associated gangrene. Following sympathectomy 14 patients had rapid healing of the ulcerations. Nine others were improved but the healing was delayed. Results in these 23 patients were considered satisfactory and constituted 57.5 per cent of the group. The remaining patients received little if any benefits from operation. Many of these fell into the group that eventually had amputations. It is of interest to note that one patient who underwent lumbar sympathectomy in this group returned to the hospital one year later with far advanced arteriosclerotic involvement of the opposite leg that necessitated amputation. The sympathectomized limb had healed promptly after operation and was in good condition at the time of readmission.

Gangrene (Table VIII)—Gangrenous involvement in sympathectomized patients for the most part was localized to the toes. In only 5 cases was the foot involved. Twenty-eight (70.0 per cent) of the 40 cases with gangrene had no further loss of tissue substance following lumbar sympathectomy. The process was arrested permanently. Eleven patients obtained no benefit and underwent subsequent amputation.

TABLE VIII RESPONSE TO LUMBAR SYMPATHECTOMY OF PATIENTS WITH ARTERIOSCLEROTIC GANGRENE

Number of patients	40
No further loss of substance following operation	28
Subsequent amputation	11
Postoperative death	1

Seventy per cent of the 63 patients who underwent sympathectomy obtained degrees of alleviation of symptoms ranging from complete amelioration to slight but significant improvement. Eleven underwent eventual amputation obtaining no help from sympathectomy (17.5 per cent). There was one death in the series—a mortality rate of 1.6 per cent. It was due to myocardial infarction on the fourteenth postoperative day.

Sympathectomy in Patients With Arteriosclerotic Vascular Insufficiency Associated With Diabetes Mellitus—There remains little doubt that diabetes mellitus accentuates the natural degenerative changes in the arteries concomitant with advancing age. As previously noted more than 80 per cent of the 21 cases of diabetes mellitus in this series were poorly controlled, uncontrolled or undiagnosed at the time of first admission. Table IX presents in detail the general status on admission and the results following lumbar sympathectomy in these diabetic patients after adequate control had been established. The results in this group were surprisingly good. Seventy-six per cent of the results were classified as either excellent or good, comparing favorably with the results of the whole group. Four had subsequent amputation.

The average age of this group of diabetic patients was 54.6 years as compared with 59.2 years for the whole series. The good results obtained in diabetic patients suggest that despite the fact that the more severe arteriosclerotic process produces an earlier onset of symptoms, the arterial tree retains a functional vascular component compatible with its chronologic age.

TABLE IV. DIABETES MELLITUS WITH PERIPHERAL ARTERIOSCLEROSIS OBLITERANS. ANALYSIS OF GENERAL STATUS ON ADMISSION AND RESULT FOLLOWING SYMPATHECTOMY

NO	AGE (YE)	SEX	CONTROL	ULCERATION	GANGRENE	RESPONSE TO SYMPATHECTOMY		RESULT
						ULCER	GANGRENE	
1	61	F	Uncontrolled	+	+	Healed	Arrested	Excellent
2	63	F	Controlled	Multiple	0	Healed	0	Excellent
3	67	F	Poorly controlled	0	+	Amputation		Poor
4	65	M	Controlled	0	+	Death	1 0	Death
5	62	M	Poorly controlled	+	+	Improved	Arrested	Good
6	53	M	Poorly controlled	+	+	Healed	Arrested	Excellent
7	58	F	Uncontrolled	+	+	Improved	Arrested	Excellent
8	56	F	Poorly controlled	+	+	Delayed healing	Arrested	Good
9	60	M	Poorly controlled	+	+	Healed	Arrested	Excellent
10	51	F	Poorly controlled	Multiple	+	Healed	Arrested	Excellent
11	55	F	Uncontrolled	0	+	Mainly prophylactic		Good
12	55	M	Uncontrolled	0	0	Mainly prophylactic		Good
13	71	M	Uncontrolled	+	0	Healed		Excellent
14	54	M	Uncontrolled	+	+	Delayed healing	Arrested	Excellent
15	69	M	Uncontrolled	+	+	Healed	Amputation	Poor
16	32	M	Uncontrolled	+	+	Delayed healing	Arrested	Good
17	71	F	Uncontrolled	0	+	1	Arrested	Excellent
18	75	M	Uncontrolled	+	+	Persisted	Amputated	Poor
19	54	M	Poorly controlled	+	+			Poor
20	58	M	Controlled	+	0	Delayed healing		Good
21	60	F	Controlled	0	+		Arrested	Excellent

The Effect of the Use of Tobacco in Patients With Peripheral Arterial Arteriosclerotic Insufficiency (Table V)—Thirty-six patients were using tobacco in some form when first seen at the hospital. Eight professed to be nonusers, while no reliable record was available in 19. Nineteen patients claimed to have ceased smoking following operation. Fifteen obtained a good or excellent response. Only one patient had a poor result. Two patients refused to stop smoking. One of them was well one year later with an excellent result. The second was adjudged to be in a satisfactory condition one year following sympathectomy that resulted in the arresting of the gangrene.

Of the nonusers of tobacco, excellent results were obtained in 4, another showed improvement in the ulcer and arrested gangrene, while 3 eventually had amputations.

TABLE V. RESULTS OBTAINED FROM LIMB SYMPATHECTOMY IN RELATION TO THE USE OF TOBACCO

Using tobacco in some form when first seen	36
Nonusers of tobacco	8
No reliable record	19
Claiming to have ceased smoking after sympathectomy	19
Excellent response	14
Good response	4
Poor response	1
Patients refusing to cease smoking	2
Well one year later with excellent result	1
Arrested gangrene, condition satisfactory one year later	1
Nonusers of tobacco	8
Excellent or good results	5
Subsequent amputations	3

Although this series is too small to evaluate the effect of tobacco in these patients with arteriosclerotic arterial insufficiency, no significant deleterious effects of tobacco could be observed when smokers and nonsmokers were compared. However, it is of interest to note that 18 out of 19 patients who ceased smoking, following sympathectomy, obtained good results.

DISCUSSION

As stated previously this group of patients represents individuals with far advanced arteriosclerotic vascular disease. The routine conservative measures of treatment had been exhausted in many of them. It was not anticipated that all of this group would greatly benefit by operation. It was hoped by careful study of this "last chance" group of patients that certain criteria could be obtained as a guide in estimating with reasonable accuracy, patients who could expect beneficial result, those in whom little benefit could be expected and lastly those in whom surgery was contraindicated because of probable unfavorable sequelae.

Greater recognition is being given to the fact that a surprisingly large number of individuals suffering from occlusive disease of the peripheral vessels have a superimposed factor of vasospasm or abnormal vasoconstriction that can be demonstrated by blockade of the lumbar sympathetic chain. It must be clearly established that the term vasospasm means an abnormal degree of vasoconstriction accompanied by clinical evidence: visual and tactile or coldness, cyanosis, mottling and sweating and also a frequent subjective complaint of pain. Vasospasm is an observable and palpable phenomenon whose presence is further verified by demonstrative release of vasoconstrictor tone. The term is greatly misused in the medical literature. Trimble, Cheney and Moses believed that almost every case of arteriosclerotic peripheral vascular disease has a functional spastic factor. It is also a well recognized fact that although careful preoperative blocking of the sympathetic chain may provide little or no evidence that beneficial effects would be obtained from sympathectomy. Subsequent operation at times produces a warm foot, an increase in walking distance and dramatic relief of pain suggesting that even a small improvement in circulation or altered tissue metabolic requirements may change the prognosis considerably. Harris was in accord with this conclusion. He stated that although preoperative tests indicate little or no vasospasm to be present many cases can be improved by sympathectomy. Such findings suggest that the factor of tone plus sympathectomy may produce results not expected from sympathetic block alone.

Vasospasm alone, however, cannot account for all of the beneficial effects obtained by elimination of sympathetic tone. This is substantiated by the observation that often a year is necessary before the maximum benefits of operation will have been obtained. The collateral arterial network will hypertrophy in response to an increase in the volume of blood flow through it. Furthermore, an increase in the volume of blood flow through an ischemic part will follow obliteration of small vessel tone and hypertrophy of the capillary network which may result from release of vasoconstriction after sympathectomy.

Previous reports^{1, 2, 3} have emphasized the desirability of demonstrating, prior to sympathectomy, a residual functional component of the arterial tree manifested primarily by increased digital temperature following lumbar block. This is undoubtedly correct in vascular disease in which vasospasm alone is responsible for the patient's symptoms. In the light of our experiences however, it is felt that in arteriosclerotic vascular disease the importance of the presence or absence of a digital thermal response following lumbar block has been overemphasized. The absence of a digital thermal response is not a contraindication to operation. Rigid adherence to the policy that sympathectomy should be limited to individuals presenting an increased thermal response following lumbar block will exclude many patients in whom beneficial results will follow lumbar ganglionectomy.

Careful study of this group has been done in an attempt to identify in directions for and contraindications to lumbar sympathectomy. Definite contraindications do exist. They are (1) severe cerebral cardiac, or renal involvement (2) paradoxical response to lumbar block that is a drop in digital temperature or an aggravation of the patient's symptoms (3) a rapidly progressing process with widespread arterial involvement (4) far advanced atrophy of the involved extremity with skeletonization (5) constant intractable pain.

Indications for sympathectomy exist primarily in the lack of contraindication to operation. The following are important nevertheless in selecting suitable patients: (1) subjective or objective response to lumbar sympathetic block (2) lack of widespread arterial involvement with slowly progressive vascular changes (3) prophylaxis in patients with contralateral amputation. This is now being done routinely in cases in which specific contraindications do not exist (4) as a measure of last resort after other forms of therapy have failed to arrest the process.

Sympathectomy has proved to be a relatively safe operation in this group of patients who are usually considered poor surgical risks. Only one death has occurred in 63 operations a mortality rate of 1.6 per cent. Complications the majority of which are peculiar to sympathectomy in arteriosclerotic vascular insufficiency were observed in 14 patients.

Vascular Complications (Table VI).—Death occurred on the fourteenth postoperative day in one patient from acute myocardial infarction. A second patient had an exacerbation of known coronary occlusive disease following operation. His condition one week later was satisfactory.

TABLE VI COMPLICATIONS AND SEQUELAE TO LUMBAR SYMPATHECTOMY FOR ARTERIOCLEROTIC PERIPHERAL VASCULAR DISEASE

Wound Infection—Severe wound infections complicated five cases. Four out of five of these patients had diabetes mellitus with ulceration and gangrene.

Paradoxical Gangrene—Atlas¹ has called attention to the occlusal rapid onset of gangrene following sympathectomy. This phenomenon has also been commented upon extensively by Freeman, Leeds and Gardner.² Two mechanisms are thought to operate simultaneously in the augmentation of the ischemia and resultant gangrene in these cases. (1) Due to destruction of the vasomotor control over the arteriovenous anastomoses in the skin there is diversion of blood directly from the arterial to the venous side of the anastomosis without passing into the distal capillary beds. Although there may be a rise in skin temperature, actually there results a decrease in the nutrient capillary flow, (2) obliteration of vascular tone results in lowering of the effective pressure necessary to drive blood into the nutrient capillaries by decreasing peripheral resistance.

We have observed gangrene with rapid onset following sympathectomy in two cases. One case came to amputation. In the second the gangrenous process underwent spontaneous arrest. Amputation was not necessary and the ultimate result was considered satisfactory.

Delayed Congestive Syndrome—Five patients developed a delayed swelling of the sympathectomized leg not unlike the clinical picture presented by chronic thrombophlebitis. This peculiar syndrome is prone to develop following sympathectomy in patients with arteriosclerosis obliterans who also have clinically evident phlebosclerosis. The superficial veins are more apparent in this type of patient but are not necessarily varicose veins. Following sympathectomy over a period of one to three months the patient develops congestive phenomena. This is characterized by a soft pitting edema and early stasis changes involving the lower part of the leg. The direction of flow in the superficial sclerotic veins is rapidly upward. The impression is gained that the arterial inflow and venous return are minimally disproportionate. Supportive therapy consisting of rest, elevation and compression bandages fails to relieve the patient. The condition slowly regresses as the sclerotic veins become better able to return the increased flow into the leg. Patients who have developed this peculiar congestive syndrome have had good results from sympathectomy in 3 of the 5 cases. Two had poor results, subsequent amputation being necessary.

Postoperative Neuralgia—A neuralgic type of pain involving the posterior and lateral aspects of the thigh of the sympathectomized leg has been observed in occasional patients in this series. Onset of the pain occurs during the first seven postoperative days. It is constant, severe and prevents the patient from sleeping. It has been described as more severe than rest pain or intermittent claudication. Fortunately the duration of this complication has never been observed to be greater than two weeks. It responds satisfactorily to bed rest and analgesics. This phenomenon is apparently due to irritation of sensory nerves innervating these skin areas. The mechanism whereby these nerves are abnormally stimulated is not always evident but the most probable cause is operative trauma.

SUMMARY

1 The early results of 63 patients submitted to lumbar sympathectomy for far advanced obliterative arteriosclerotic vascular disease have been presented

2 Follow up studies over a two and one half year period reveal that 70 per cent of the group obtained some measure of alleviation of symptoms following operation

3 Indications for and contraindications to, sympathectomy in this group of patients have been presented and discussed. It is not possible to establish indications for operation by statistical methods. Great care must be exercised in choice of patients if good results are to be consistently obtained

4 The deleterious effects of sympathectomy for arteriosclerotic vascular insufficiency have been noted and discussed

REFERENCES

- 1 Atlas I N Lumbar Sympathectomy in the Treatment of Selected Cases of Peripheral Arteriosclerotic Disease Am Heart J 22: 543 1941
- 2 Atlas L N Lumbar Sympathectomy in the Treatment of Selected Cases of Peripheral

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THE ARTERIOSCLEROTIC POPLITEAL ANEURYSM

A REPORT OF FOURTEEN PATIENTS TREATED BY A PRELIMINARY
LUMBAR SYMPATHETIC GANGLIOTOMY AND ANEURISMECTOMY

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SPONTANEOUS aneurysms of the popliteal artery are the most common aneurysms which are curable by surgical measures. The true incidence of this disease is probably not given in any available statistics but according to Crisp¹ this blood vessel was involved more frequently than any other artery of the body except the thoracic aorta. In a series of 551 cases of aneurysm he collected in 1847 he found that 137 or 25 per cent were of the popliteal artery whereas 175 or 32 per cent were of the thoracic aorta the most common site of aneurysm in the body. Mitas² in 1920 reported the involvement of the popliteal artery in 154 or 53.2 per cent of 289 cases of aneurysm which had been operated upon by his technique of endoneurismorrhaphy.

Syphilis plays an important role in the etiology of some aneurysms, but many instances are encountered without evidence of this disease in which arteriosclerosis is the chief etiological factor. The luetic type of aneurysm occurs usually in patients under the age of 50 years whereas the arteriosclerotic more frequently in those past the age of 60 years. The reports in the surgical literature except for Lally's³ recent one have not directed particular attention to the arteriosclerotic type of aneurysm. In a group of 42 patients admitted to the surgical wards of the Massachusetts General Hospital for the forty year period from 1908 to 1947 arteriosclerosis was the chief etiological factor in 31 or approximately 74 per cent of the cases. It also played a role undoubtedly in 4 of the patients with lues whose ages were 57, 57, 58 and 66 years. An analysis of this group of 42 patients reveals that the luetic type has been occurring less frequently whereas the arteriosclerotic is becoming more common. In the first decade of this period from 1908 to 1917 there were 4 syphilitic aneurysms and no arteriosclerotic ones. In the next decade 1918 to 1927 there were 4 cases, 1 or 25 per cent was arteriosclerotic and 3 or 75 per cent were luetic. From 1928 to 1937 9 patients were seen, 5 or 55 per cent were arteriosclerotic and 4 or 45 per cent were luetic. During the last decade 1938 to 1947, it is of extreme interest that 25 patients were seen and all or 100 per cent of them were arteriosclerotic none were luetic (Fig. 1). The ages in the arteriosclerotic group ranged from 43 to 82 years with a mean age of 65 years while in the luetic group they were from 30 to 66 years with a mean age of 47.7 years. Tabulated in decades according to years in the

¹ Read at the second annual meeting of the Society for Vascular Surgery, Chicago, Ill. June 6, 1913.

THE ARTERIOSCLEROTIC POPLITEAL ANEURYSM

A REPORT OF FOURTEEN PATIENTS TREATED BY A PRELIMINARY
LUMBAR SYMPATHETIC GANGLIONECTOMY AND ANEURYSMECTOMY

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SPONTANEOUS aneurysms of the popliteal artery are the most common aneurysms which are curable by surgical measures. The true incidence of this disease is probably not given in any available statistics but according to Crisp¹ this blood vessel was involved more frequently than any other artery of the body except the thoracic aorta. In a series of 511 cases of aneurysm he collected in 1847 he found that 137 or 25 per cent were of the popliteal artery whereas 175 or 32 per cent were of the thoracic aorta the most common site of aneurysm in the body. Matas² in 1920 reported the involvement of the popliteal artery in 154 or 53.2 per cent of 289 cases of aneurysm which had been operated upon by his technique of endoaneurysmorrhaphy.

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Read at the second annual meeting of the Society for Vascular Surgery Chicago Ill
June 6 1949

arteriosclerotic group 3 were in the fifth decade 6 in the sixth 10 in the seventh 11 in the eighth, and 1 in the ninth, whereas in the luetic group 4 were in the fourth decade 2 in the fifth, 4 in the sixth and 1 in the seventh (Fig. 2). This increased incidence of the arteriosclerotic popliteal aneurysm especially during the last decade 1938 to 1947, is apparently due to the fact that the span of human life is increasing and people are living to an older age, when they

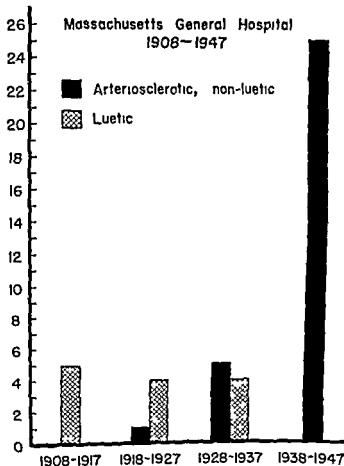


Fig. 1—Graph showing incidence of arteriosclerotic and luetic popliteal aneurysm in 4 patients admitted to the Massachusetts General Hospital in the forty year period from 1908 to 1947 and arranged according to decades.

are more subject to degenerative vascular diseases. According to Ivy, the life expectancy in 1900 was 49 years whereas in 1945 it was 66 years. He also pointed out that 77 per cent of the population in the United States, or almost 11 million persons, are now over 65 years of age and by 1960 there will be 9 per cent over this age. It seems therefore from these statistics that this type of vascular lesion will be seen with a still increasing frequency.

The surgical treatment of aneurysms dates back many centuries. Antyllus, a Roman surgeon in the third century, according to Henry,⁵ and the fourth century according to Treves,⁶ developed the method of tying the artery above and below the aneurysmal sac and then evacuating the contents. Philagrius of Macedon in the fourth century, according to Ransahoff,⁷ first practiced extirpation of an aneurysm. Guthrie⁸ writing in 1830 stated that Aetius in the sixth century recommended ligation and division of the artery proximal to the aneurysm then opening of the sac and intrasaccular ligation of the artery at the distal end of the sac. The same author stated that Paulus in the

Massachusetts General Hospital 1908-1947

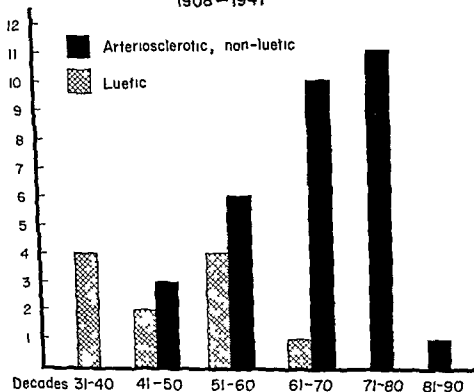


Fig. 1.—Graph showing ages in years arranged according to decades of 49 patients with arteriosclerotic and luebic popliteal aneurysms admitted to the Massachusetts General Hospital in the forty year period from 1908 to 1947.

seventh century advised extirpation of the aneurysm, having previously applied a ligature above and below it. Surgery of aneurysms according to Guthrie⁸ remained in this state until the sixteenth century when Guillemeau advised proximal ligation opening of the sac removing the intrasaccular thrombi and filling it with lint leaving it to heal by the usual processes of suppuration and cicatrization. Purmann in the seventeenth century according to Ransahoff⁷ rediscovered the method of treatment by extirpation, first described by Philagrius. Anel in the sixteenth century, according to Ottley,⁹

tied the artery immediately above the sac but left it unopened. Hunter, in the eighteenth century, developed his method of proximal ligation some distance from the sac in what is now known as Hunter's canal for the treatment of popliteal aneurysms. His method was first described by his assistant Home in 1786¹⁰ and again in 1793.¹¹ Again the surgery of aneurysms remained in this state until Matas,¹² in the first part of the twentieth century, described his method of endoaneurysmorrhaphy which since then has been considered the standard method of treatment. He was the first to stress the importance of building up the collateral circulation before operating on the aneurysm. According to Matas,¹³ gangrene followed the Hunterian operation, or proximal ligation in 10.5 per cent of the cases; the Antylus method or proximal and distal ligation with evacuation of the sac, in 8.33 per cent; the Philagrius' or Purmann's method of extirpation of the sac in 5.71 per cent. Matas² in 1920 reviewing 154 cases of popliteal aneurysm treated by his method of endoaneurysmorrhaphy reported an incidence of gangrene in 8 cases or 5.2 per cent. From these statistics it is apparent that regardless of which method was used to cure a popliteal aneurysm a certain number of extremities developed gangrene. It was natural, therefore, that some other method of treatment should be sought for to eliminate it in all the cases if possible.

The next important advance in the surgical treatment of aneurysms resulted from the experimental work of Mulvihill and Harvey¹⁴ in 1931 when they demonstrated the beneficial effect of sympathetic ganglionectomy to the extremity after acute arterial occlusion. Cane⁵ in 1934 was the first to utilize this method in the treatment of an aneurysm of the common iliac artery. Bird¹⁵ in 1935 reported the first popliteal aneurysm treated with success by a preliminary lumbar sympathetic ganglionectomy followed in four weeks by an obliterative endoaneurysmorrhaphy. Since then others have confirmed the beneficial results obtained by preliminary sympathetic ganglionectomy in the treatment of aneurysms of the lower extremity. Lerche and Froehlich¹ in 1939 utilized it in an occluded aneurysm of the femoral artery. Cane¹⁵ in 1940 reported its use in 15 cases of aneurysmorrhaphy and again in 1943¹⁶ recommended it in the management of traumatic arterial aneurysms. Richards and Fairmonth² in 1942 performed a lumbar sympathectomy three weeks prior to extirpation of a popliteal aneurysm with success. Lill³ in 1946 reported 3 popliteal aneurysms treated successfully by sympathectomy and aneurysmorrhaphy.

The purpose of this paper is to report 14 patients with arteriosclerotic type of popliteal aneurysm admitted to the surgical wards of the Massachusetts General Hospital during the five year period 1942 to 1947 and to describe the method of treatment utilizing a two stage operative procedure: first a preliminary lumbar sympathectomy; later an aneurysmectomy. The youngest patient was 49 years of age and the oldest 79 years. The youngest patient was in the fifth decade and the oldest 49 years. Three were in the sixth decade, aged 54 and 56 years; 5 were in the seventh decade, aged 61, 63, 64, 68 and 69 years; 5 were in the eighth

decade, aged 71, 74, 74, 75 and 79 years. There were 13 men and 1 woman in this group of patients. The aneurysms were unilateral in all the patients except one in whom they were bilateral so that there were a total of 15 in the 14 patients 7 in the right extremity and 8 in the left. The one patient with bilateral aneurysms lost the right leg from gangrene because of thrombosis of the aneurysm before surgical measures could be instituted to save it. For that reason this aneurysm will not be considered further in this report. Aneurysms developed spontaneously in 11 patients and followed trauma in 3 of them. One patient gave a history of a severe fall and wrenched knee two weeks before the aneurysm was noticed. Another had dislocated his knee seven years previously and the other had received a severe blow four months prior in the popliteal space. Syphilis did not play a role in the etiology of any since the blood Hinton or Wassermann tests were negative in all the patients. Swellings in the popliteal space had been noted by 11 patients and was unobserved by 3. The duration that the aneurysms had been noted by the patients varied from one week to five years. In the majority it was eight weeks or less. The predominant symptom and complaint was local pain in the popliteal space observed in 11 patients. The other 3 were not conscious of the aneurysm and did not complain of pain. These were detected in routine examinations of their extremities. The pain developed suddenly in 4 instances secondary to a sudden increase in the size of the aneurysm and in 2 cases as the result of a rupture of the sac with the formation of a false aneurysm. The size of the aneurysmal sac varied from 3 by 5 cm. the smallest to 15 by 20 the largest. Twelve were fusiform in shape and 2 were saccular with large associated false aneurysms. Arterial pulsations were detectable in all the aneurysms and in addition in the dorsalis pedis artery in 4 of the extremities and in the posterior tibial artery in 6 instances. All 3 of these arterial pulsations were present in 2 of the extremities. Intermittent claudication was a symptom in 4 patients varying from one to ten years in duration. These observations indicate that in most of the patients there was evidence of obliterative arterial disease distal to the aneurysm but none showed any evidence of gangrene in the extremities. Pathologic examination of all the aneurysms revealed a laminated blood clot consisting of partially organized and fresh thrombi (Fig. 3). In most instances some of it was so loosely attached that if it had been dislodged embolism of the arteries distal to the aneurysm would have occurred with resultant gangrene of the extremity.

The aneurysmectomies were performed seven to eleven days after the sympathectomies. Gangrene of the extremity did not develop in any of the cases and only in one instance did the circulation seem precarious for a few days following the aneurysmectomy. Intermittent venous occlusion²¹ was used in this instance until the circulation was adequate. This patient was aged 74 years. There were pulsations in the dorsalis pedis and posterior tibial arteries before operation indicating that the collateral circulation of the lower leg and foot had not developed to the extent that it had in most of the other patients whose peripheral arteries had been previously occluded due to

A

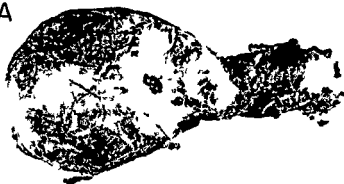


Fig. 1. A. Photomicrograph of the histological section of the distal arteries.

B



Fig. 2. B. Photomicrograph of the histological section of the distal arteries after removal of the artery from the histological section.

arteriosclerosis so that the sudden surgical occlusion of the popliteal artery at the time of the aneurysmectomy reduced the circulation distal to this point to a precarious level. It is believed that without the preliminary sympathectomy the extremity probably would have developed gangrene. One patient died following the lumbar sympathectomy, a mortality rate of 7 per cent. The cause of death in this case was a combination of postoperative retroperitoneal hemorrhage and heart failure from severe coronary heart disease. The former was thought, in part at least, to be attributable to the postoperative use of intravenous heparin to prevent thrombosis of the popliteal aneurysm after the sympathectomy. Since then in other patients it has not been used following the sympathectomy. This patient was a poor selection for the operation because the post mortem examination showed a previous coronary thrombosis had caused a severe infarction of the left ventricle. None of the 13 patients who survived the operative procedures developed gangrene and both the life of the patient and the limb were preserved in all cases, or 93 per cent of the entire group.

The method of treatment that is recommended is a two stage operative procedure to include a preliminary lumbar sympathetic ganglionectomy which is followed in approximately ten days by an aneurysmectomy. Certain points in the operative management of these cases by this method need particular emphasis. A careful evaluation of the patient's cardiovascular condition is imperative and should be done before the sympathectomy. The staging of the operative procedures is of extreme importance because it permits the interruption of the popliteal artery, after elimination of the vasoconstrictor influence of the sympathetic nervous system and after stabilization of the vascular system in its maximum degree of vasodilatation as demonstrated by Smithwick.² Furthermore both procedures should not be done at the same operation because of the danger of surgical shock with a drop in the arterial blood pressure. Even if the patient survived the extremity would likely suffer irreversible vascular changes with resulting gangrene because the degree of hypotension distal to the interruption of the popliteal artery would be relatively greater than in the remainder of the arterial system. Ether inhalation anesthesia was used for the lumbar sympathetic ganglionectomy, since it is considered the safest method in these elderly arteriosclerotic patients. Spinal anesthesia was used preferably for the aneurysmectomy because with the low level of anesthesia required for operating at the knee the patient's systemic blood pressure could be more readily maintained than with a general anesthetic. In addition the vasoconstrictor influence of ether anesthesia on an extremity previously sympathectomized was eliminated. The sympathectomy was performed through an extraperitoneal exposure. The flank type of incision described by Smithwick²¹ was used to facilitate the removal of the first, second, and third lumbar ganglia so that the entire thigh as well as the lower leg would be sympathectomized.

A limb tourniquet should not be used to control the arterial inflow to the extremity. First, because of the danger of fracturing an arteriosclerotic femoral

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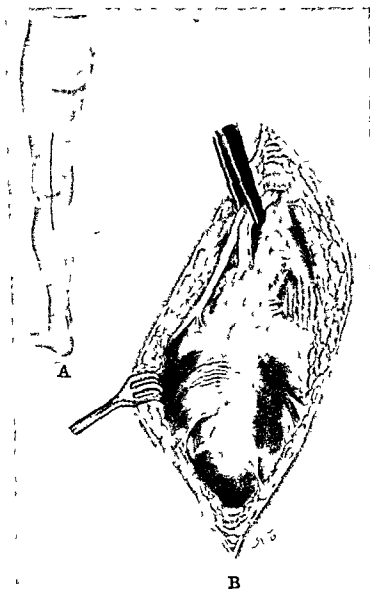


B



Fig 3—4. Photograph of a double arteriosclerotic popliteal aneurysm removed from a man aged 71 years. Not how clean the aneurysm has been resected. *B* Photograph of the same specimen opened showing the oil partially organized and fresh thrombi almost filling the aneurysmal sac. The latter if distended may produce embolism of the distal arteries with resulting gangrene of the extremity.

occur because blood still can circulate through the collateral channels the same ones that the limb will depend on thereafter for its circulation. Sixth the observation of arterial bleeding from the distal end of the popliteal artery after extirpation of the aneurysm the so called Henle Coenen sign, will demonstrate to the surgeon the adequacy of the collateral circulation and assure him of the viability of the extremity.



B

Fig. —An artistic drawing showing (1) the long vertical type of incision extending sufficiently proximal and distal to the aneurysm to give easy access to the afferent and efferent in order to avoid damage to them.

artery. Second, it shuts off all the arterial inflow to the extremity during the operation so that the collateral arteries in the operative field are not readily recognized and preserved. Third on release of the tourniquet, the state of so called "tourniquet shock" may develop with a drop in the systemic blood pressure which would be serious to both the patient and the limb. The application of a modified Bethune lung tourniquet clamp (Fig. 4) to the popliteal artery proximal and distal to the aneurysm was utilized for the control of the arterial inflow to the aneurysm. This method of arterial control is recommended for a number of reasons. First, it gives the surgeon peace of mind to perform a careful dissection close to the aneurysm so that the collateral arteries



A



B

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will not be damaged since uncontrollable hemorrhage will not occur even if the aneurysmal sac is inadvertently opened. Second with the main arterial inflow to the aneurysm shut off both proximally and distally a thrombus from it if dislodged during the further dissection of the sac will not be carried distalward to occlude the arterial system. Third the collateral blood supply about the knee and to the lower leg and foot is not shut off during the operation so that necessity for haste during the dissection is eliminated. Fourth the collateral arteries in the operative field since they still pulsate can be recognized and preserved. Fifth the so called "tourniquet shock" which may develop after the removal of a tourniquet applied to the thigh does not

muscles. Great care is taken not to damage the superior genicular arteries if they arise above the aneurysm and also the highest genicular artery which arises from the distal part of the superficial femoral artery. Modified Bethune long tourniquet clamps (Fig 7) are applied to the popliteal artery about 2 cm proximal and distal to the aneurysm and the vessels occluded during the remainder of the dissection. The aneurysmal sac is dissected free with extreme

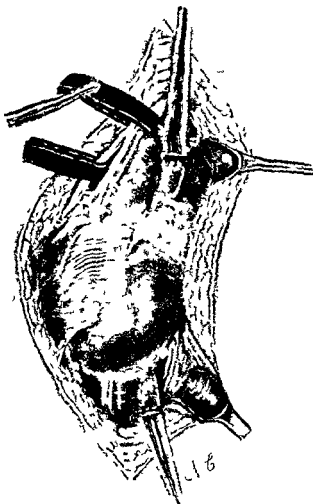


Fig. —An artistic drawing showing the aneurysm, the sciatic common peroneal and posterior tibial nerve. The latter retracted with wide rubber band. Note the tourniquet clamp on the popliteal artery proximal and distal to the aneurysm. The popliteal vein lies on the aneurysmal sac to which it is intimately attached.

care staying as close to it as possible in developing a cleavage plane between it and the tissues of the popliteal space. In this manner the tributaries arising from the aneurysm may be ligated at their origin and the arteries of the collateral blood supply will not be damaged any more than if they were ligated

Adequate exposure of the aneurysm its main afferent and efferent arteries is essential and cannot be overemphasized. It is best obtained by an incision which overlies and parallels these blood vessels. For these reasons a vertical incision is recommended, which extends proximal to the aneurysm into the thigh, and distal to it into the upper part of the lower leg (Fig 5). The crease in the popliteal space is necessarily crossed by the incision, but with careful closure of it, using fine nonabsorbable interrupted sutures to the popliteal fascia and interrupted vertical mattress sutures to the skin, contractures or keloid scars have been avoided in all the extremities (Fig 6).



Fig 5.—A photograph showing a healed vertical type of incision without contracture or keloid formation in a patient 11 years old taken 45 years after the aneurysmectomy.

When the incision is completed towels are sutured to the skin edges to isolate the operative field from skin contamination during the operation. The great nerves the sciatic common peroneal and posterior tibial nerves are first dissected free. The latter is often intimately attached to the aneurysmal sac. After isolating them a soft wide thin rubber band is placed around each to mark them for retraction is necessary during the further dissection (Fig 5). If these precautions are not taken the nerves may be injured by retractors with resulting partial paralysis. Next the popliteal artery is exposed proximal to the aneurysm between theiceps femoris and the semimembranosus.

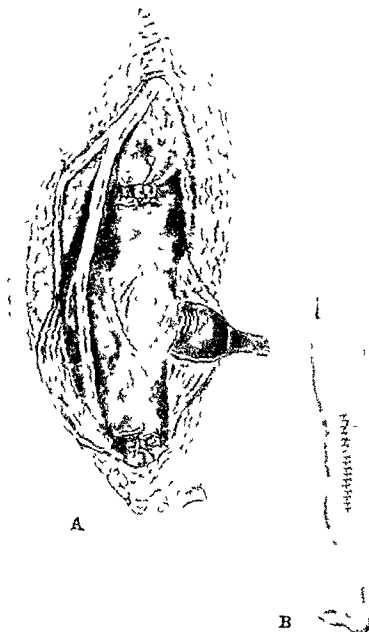


Fig. 9.—In with its drainage to show (1) the operative field with the aneurysm exposed and the great vessels intact, the proximal and distal ends of the posterior artery and vein fully ligated and (2) the incision closed with its drainage with fine interrupted cotton or silk sutures to the posterior (1) and interrupted vertical mattress silk sutures to the skin.

by the intrasaccular method. The popliteal vein as a rule is intimately adherent and sometimes incorporated in the posterior wall of the aneurysm (Fig 7). No attempt should be made to preserve it unless it lies free, as occasionally is the case with a very small aneurysm arising from the anterior wall of the popliteal artery. This is contrary to Matis' advice¹³ as he stated 'I believe that preservation of the (popliteal) vein is a matter of decided importance to the viability of the limb and its sacrifice when unavoidable must always be a source of anxiety and apprehension.' There seems little support to this view in the cases of this report since the popliteal vein was resected in 12 of them without serious effect to the extremities. In the remaining one it lay free of a small aneurysm so it was not interrupted but the superficial femoral vein was interrupted to prevent thromboembolism.

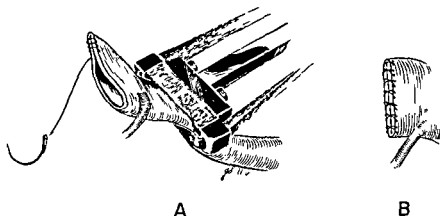


Fig 8—An artistic drawing showing the suture in the act of closing the popliteal artery to preserve a collateral artery. A The tourniquet clamp is still closed with the over and over suture started. B The closure completed with a double row of suture with preservation of the collateral artery.

The next step is to ligate the proximal and distal ends of the popliteal artery and vein. This should be performed with nonabsorbable ligature material first ligating the vessel and then placing a transfixion ligature in the cuff distal to the primary ligation. An alternate method of closing either or both ends of the popliteal artery has been used to preserve collateral arteries that arise within 1 cm of them. Adequate hemostasis under these circumstances is obtained by closing the end of the popliteal artery with two rows of a running suture of 0000 arterial silk a method similar to the one described by Murray and Jones²⁴ (Fig 9). In this manner the collateral vessel may be saved since only 1 to 2 mm of the popliteal artery are used whereas with the usual ligature closure about 1 cm is necessary which would also occlude the collateral artery. After a final inspection of the great nerves and blood vessels the wound is closed in two layers without drainage (Fig 9). Interrupted sutures of fine silk or cotton are used in the popliteal fascia and the skin is closed with interrupted vertical mattress sutures of silk. This latter

Excision of an aneurysm is one of the oldest methods of surgical treatment for this condition. Philagrius of Macedon in the fourth century first practiced it, then it was discarded but later rediscovered by Paulus⁵ in the seventh century and by Purmann⁷ in the seventeenth century. It had many advocates in the nineteenth century until Mats¹² described his method of endoaneurysmorrhaphy at the beginning of the twentieth century. Now, again, it is recommended as the most satisfactory method of treatment for the arteriosclerotic type of popliteal aneurysm, when it is combined with a preliminary sympathetic ganglionectomy. Extirpation of the aneurysm is preferred in this type to the Mats obliterative endoaneurysmorrhaphy, because of the difficulty encountered frequently in obliterating the aneurysmal sac due to the rigidity of its walls from arteriosclerosis and calcification. It is considered also to be a safer method for this type of aneurysm than the ingenious restorative endoaneurysmorrhaphy by a veingraft inlay described recently by Blakemore²³ because of the marked arteriosclerosis of the popliteal artery both proximal and distal to the aneurysm which makes a satisfactory nonsuture type of anastomosis difficult to perform.

It is believed that any patient presenting an arteriosclerotic popliteal aneurysm irrespective of age should be considered a candidate for the surgical removal of it preferably by a preliminary sympathectomy and followed later by an aneurysmectomy unless the patient's cardiac condition contraindicates such treatment or if the aneurysm has become thrombosed spontaneously with resulting gangrene of the extremity. The presence of multiple aneurysms of a similar nature in other large arteries of the body may also be a contraindication. The serious effect of this condition on the life of the patient and the extremity in untreated cases it is believed makes this radical view justifiable. It is well demonstrated by the outcome in a group of 15 patients similar to the one in this report who were admitted to the Massachusetts General Hospital from 1929 to 1947 because of unilateral or bilateral arteriosclerotic popliteal aneurysms that were not treated by surgery. The mean age of this group was 66.7 years; the youngest patient was aged 48 years and the oldest was 82 years. Seven of the patients had bilateral aneurysms making a total of 22 extremities with popliteal aneurysms. Eleven patients or 50 per cent had gangrene of the extremities on admission to the hospital and another 6 or 27 per cent, developed it in the hospital while awaiting surgery. Low thigh amputations were performed on all 17 extremities making a limb mortality of 77 per cent. This dire effect to the extremity in untreated cases has been emphasized recently in the literature by others including Blakemore,² Flemming,²⁴ Hufnagel,²⁵ Keynes and Morel,²⁶ Lilli,² Theris,²¹ and Wells and associates.²² Furthermore a patient mortality rate of 26.6 per cent occurred since 4 patients died as a result of the disease following amputation of an extremity performed because of gangrene secondary to thrombosis of the aneurysm, 1 died from septicemia and the other 3 from massive pulmonary embolism. The results obtained in the 14 similar cases of arteriosclerotic popliteal aneurysm in this report, treated by a preliminary sympathetic ganglionectomy and aneurysmectomy,

type of suture is important to prevent a contracture in the scar at the crease in the popliteal space as previously stated. A posterior molded plaster splint is applied to the thigh and lower leg to keep the knee in extension. Bilateral superficial femoral vein interruptions are recommended in these patients to prevent pulmonary embolism. These should be performed preferably before the aneurysmectomy but they may also be done a day or two after it. Intravenous heparin may be used for a few days following the removal of the aneurysm to prevent arterial thrombosis in the arteries distal to the knee. The decision whether or not to use this drug depends on the degree of the collateral circulation; that is, if it is poor it is advisable to use the drug whereas if it is excellent the drug is not necessary. Following the operation the patient is placed in bed, the head of which has been elevated about six inches on blocks in order to keep the extremity a little below the level of the heart to insure a better circulation of the foot. In addition it should be kept cool to maintain the metabolism of the leg at a lower level consistent with the diminished arterial blood supply. External heat should not be applied to the lower leg and foot under any circumstances. The patients are ambulatory usually by the end of the first week and are discharged home from the hospital at the end of the second week.

DISCUSSION

Many surgeons believe that the surgical interruption of the popliteal artery as is necessary in the excision of a popliteal aneurysm may result in gangrene of the extremity. This opinion is based chiefly on the experiences of major blood vessel injuries occurring in World War I and World War II since it was observed that the popliteal artery if injured resulted in a higher incidence of gangrene than any other peripheral artery. DeBakey and Simeone⁶ reported that in a collection series of 502 popliteal artery injuries from American World War II casualties there were 364 or 72.5 per cent who lost limbs. They also reported that Ogilvie of the British Army Medical Corps stated at the Cairo Conference in 1943 that he had not seen in the course of war a single instance of ligation of the popliteal artery which was not followed by gangrene. It is to be emphasized however that conclusions regarding the results of elective surgery on the popliteal artery such as reported here for aneurysms should not be drawn from the experiences of gunshot wounds of this vessel. An analysis of the two types of wounds, the one resulting from a missile and the other from a surgeon's scalpel, reveals little analogy. There is usually with the former in addition to the popliteal artery injury a severe wound of the soft parts about the knee joint with destruction of the collateral blood vessels or occlusion of them from edema and extravasation of the blood whereas the ligation and division of it even the extirpation of the aneurysm leaves these vessels intact for the most part so that gangrene rarely will occur. Furthermore a preliminary sympathectomy in cases of elective major blood vessel surgery as described here can be performed to safeguard the extremity thereby preventing vasoconstriction of the arterial system distal to the point of the arterial interruption.

when first seen were not relieved of this complaint by the removal of the aneurysm but this symptom also was not made worse. The others at first complained of a tired feeling in the leg on exercise but did not complain of true intermittent claudication and as the years have passed it has tended to improve.

CONCLUSIONS

1 The incidence of the arteriosclerotic type of popliteal aneurysm is increasing.

2 An arteriosclerotic popliteal aneurysm, if untreated is a serious threat to the viability of the extremity and also to the life of the patient.

3 A two stage method of surgical treatment is recommended consisting of a preliminary lumbar sympathectomy followed approximately in ten days by an aneurysmectomy.

4 Fourteen patients with arteriosclerotic popliteal aneurysms the ages of whom ranged from 49 to 79 years are reported. Thirteen or 93 per cent survived and their extremities were saved utilizing this method of treatment. One patient died from postoperative hemorrhage and coronary thrombosis following the sympathectomy a mortality rate of 7 per cent.

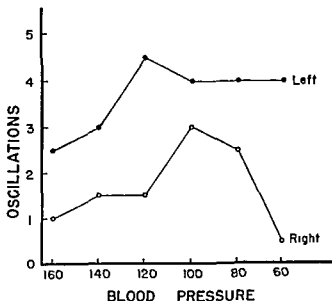
The author wishes to thank Dr. Claude L. Welch for permission to include in this group his case as well as the other 13 patients who were operated upon by the author.

REFERENCES

- 1 Craig, I. A Treatise on the Structure, Disease and Injuries of the Blood Vessels With Statistical Deduction. London 1847. J. & A. Churchill Ltd.
- 2 Math, R. Embolism morphologically. Surg., Gynec. & Obst. 30: 406, 1920.
- 3 Lilly, C. D. The Management of Aneurysm of the Lower Extremities. Ann. Surg. 123: 101, 1916.
- 4 Ivy, A. C. Drug Therapy in Degenerative Disease. J. A. M. A. 135: 900, 1948.
- 5 Henry, A. K. Some Surgical Aspects of Aneurysm. Practitioner 150: 11, 1942.
- 6 Truett, T. A Manual of Operative Surgery. Vol. 1. London 1901. Cassell & Co. Ltd.
- 7 Ranchoff, J. The Excision of Aneurysms. Ann. Surg. 19: 78, 1894.
- 8 Guthrie, C. J. Surg. 30: 14, 1900.
- 9 O'Leary, D. Thrombosis of the Popliteal Vein. The Operation for
- 10 Hume, F. An
- 11 Hume, F. An
- 12 Hume, F. An
- 13 Hume, F. An
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demonstrate what can be accomplished with modern surgical treatment. Thirteen patients and their extremities survived, a salvage of 93 per cent without evidence of gangrene. One patient died following the sympathectomy, a mortality rate of 7 per cent.

A follow up study reveals that two of the patients have died one from cirrhosis of the liver one year later and the other after fourteen months from the rupture of an atherosclerotic common iliac aneurysm. The extremities of all these patients functioned normally following the operative procedure. Eleven of them are still living and well two months to five years since discharge from the hospital. The most common postoperative complication was edema of the lower leg which developed in 5 or 38 per cent of the cases. It disappeared in 3 of them with elastic bandages, the other 2 still need some support to the extremities. It is of extreme interest that the arterial inflow to the



lower leg in 2 of the extremities is of sufficient volume to produce pulsations in the arteries of the feet. One of these, a man aged 73 years seen five years following the aneurysmectomy, has had a return of palpable pulsations in the dorsalis pedis and posterior tibial arteries of the foot. The oscillations at the ankle obtained by oscillometry, although not as great as in the other extremity, are of moderate amplitude (Fig. 10). The other patient, a man aged 58 years, had a return of pulsations in the posterior tibial artery at the ankle within four weeks after the aneurysmectomy and when last seen thirteen months later they were still present. The 4 patients who had intermittent claudication

COMPLICATIONS RESULTING FROM INJURIES TO MAJOR ARTERIES

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MANY of the complications which follow in the wake of trauma to or in the vicinity of, large arteries may come on so insidiously that the surgeon does not give proper consideration to his patient's apparently minor complaints. An untold number of extremities are sacrificed because the effects of the arterial insufficiency are not recognized until after extensive damage to the muscles has already taken place. We are convinced that many limbs and even many lives could be saved each year if all surgeons were more alert to the early signs and symptoms of these complications. Prompt diagnosis of the kind and site of the arterial injury with as little delay as possible in instituting definitive treatment should be the goal of every surgeon. Constant observation of all patients with suspected arterial injuries and the immediate correction of any secondary vasospasm which may become apparent are factors of paramount importance to the success of this type of vascular surgery.

It is our purpose in this presentation to emphasize the more common complications and to illustrate the late effects of such arterial injuries by a few selected case histories.

SECONDARY ARTERIAL SPASM

The most common complication of injuries to, or near large arteries is spasm involving some part of the artery or the entire arterial bed. Extensive arterial spasm may be brought about by a variety of injuries due to violence or to surgical operations. Sometimes there is evidence of direct trauma to the arterial wall but even more often the artery itself may be unharmed. Large arteries such as the brachial or femoral artery exhibit this phenomenon partly because of their length and exposed positions. Spasm in the artery as well as in the arterial bed is usually due to abnormal nervous reflexes since arterial thrombosis is not a common finding in the early stages of this syndrome. Intense spasm of the arteries and arterioles may last for hours or even days. The degree of arterial insufficiency which results from this superimposed vasospasm may be sufficient to bring about serious changes in the soft tissues. Peripheral arterial spasm is most severe following gunshot or crushing wounds of the extremity but may also occur after simple puncture wounds, operative procedures upon large blood vessels or injuries to large nerves. Most students of these problems agree that prolonged arterial spasm can bring about changes in the skin, nerves, muscles and joints of an extremity. The condition may show a tendency to disappear spontaneously but in most patients it persists sufficiently long to endanger the viability of the soft tissues. The simplest means of over-

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- 21 Linton R R Means of Intermittent Venous Occlusion
- 22 Smithwick R apathetic Nervous System for Peripheral 1940
- 23 Smithwick R F amputectomy for the Relief of Vascular Spasm of the Extremities New England J Med 222 699 1940
- 24 Murray C and James J N The Healing of Arteries and the Relationship to Secondary Hemorrhage SURGERY 18 64 1945
- 25 Williams A H Battle Injuries of the Arteries in World War II neurym by Amputation 9 Clin North America. 18 400 1939
- 26 Flemming C Aneurysm of Both Popliteal Arteries Lancet 1 392, 1909
- 27 Hufnagel C J Popliteal Aneurysms M Bull Vet Admin 20 86, 1943
- 28 Keynes G L and Morel M I Popliteal Aneurysm Brit J Surg 31 155 1943
- 29 Thiers F V Popliteal Aneurysms as a Cause of Peripheral Circulatory Disease With Special Study of Oscillographs as an Aid in Diagnosis SURGERY 2 327 1937
- 30 Wells A H (ofurn C F, and Walker M A Popliteal Aneurysm J A M A 106 1204 1936

wise to attempt to restore the continuity of the divided artery even though this restoration may be successful for only a few days. This is particularly true in the cases of serious hemorrhage from a severed major artery such as the popliteal artery, the femoral artery in Hunter's canal or the common carotid artery when they are associated with extensive extravasation of blood into the surrounding tissues.

Internal Hemorrhage—In general if the bleeding is not endangering the life of the patient or if the pressure of the extravasated or accumulated blood is not seriously affecting any vital function, damaging any hollow viscus or causing marked ischemia in the affected extremity, there is no need for immediate surgical intervention. A hematoma which continues to enlarge and through pressure on small collateral arteries actually impairs the arterial circulation to the extent of producing impending gangrene should be treated surgically without delay.

Secondary Hemorrhage either internal or external is rarely a complication of injury to a large artery even though the artery shows evidence of severe arteriosclerosis. If hemorrhage does occur under such conditions it should be treated as though it were primary. Most often secondary hemorrhage is the result of infection in the wound. In spite of the infection the bleeding vessel should be isolated and ligated with nonabsorbable material. No attempt should be made to cover the vessel and the wound should be left open and loosely packed with fine mesh gauze moistened with normal saline solution. When there is clinical evidence of a growing tumor at the site of the injury or more pain radiating along the course of the artery, one must suspect secondary hemorrhage. Massive bleeding into some cavity of the body may result in sudden death. Surgical exploration of the wound with definite and prompt arrest of the hemorrhage by ligation of the artery without regard to the effect upon the peripheral tissues should then be done. Packing with gauze and the application of compression bandages are of little practical value in such instances for the secondary hemorrhage will most certainly recur unless the bleeding vessels are permanently occluded by ligatures.

Secondary hemorrhage may also result from erosion of major arteries. Bone fragments or bone plates and screws used in the repair of fractures may be in contact with some major artery and the constant pulsation of the artery against the solid object may cause erosion of the arterial wall with extensive internal hemorrhage. The following case will illustrate this kind of complication.

Case 1—The patient, a 45-year-old white man, was referred to us on June 3, 1947. On April 2, 1947, he had been struck by the motor of a train and sustained a supracondylar fracture of the right femur. At the time he got to the hospital the reduction could not be held satisfactorily well with a plaster of Paris cast so screws were placed in the distal femur to hold the fragment in position. Within twenty-four hours the right foot became cold and pulseless and there was complete loss of sensation and ability to move the foot and ankle. The leg was purple and discoloration soon followed (Fig. 1). Intensive physiotherapy was begun but no improvement was noted and the patient was transferred to this hospital for amputation of the leg had to be performed and at operation it was found that most of the wall of the artery had been destroyed with the popliteal artery and the final result was the complete rupture of the wall of the artery (Fig. 1).

coming this peripheral vasoconstriction in injured extremities is by repeated novocainization of the regional sympathetic ganglia of the affected extremity.

INTRAVASCULAR INJURIES TO LOWER ARTERIES

The injection of an insoluble preparation into any major artery may give rise to serious complications. Preparations of bismuth have been injected accidentally into the gluteal artery causing intolerable pain and local areas of necrosis of the soft tissues of the buttocks. Foreign bodies are occasionally transported by these arteries and become lodged in smaller peripheral arteries.

The most frequent cause of intravascular injury is the lodgment of a blood clot which has been carried from the heart or aorta into some peripheral artery. The sudden occlusion of the intima of the peripheral artery provokes marked reflex vasoconstriction in the entire vascular bed of the extremity. The stantiation of blood brought about by this vasoconstriction favors progressive arterial thrombosis.

We believe that acute arterial occlusion should be considered a real emergency and every method of promoting adequate circulation through the collateral arterial pathways should be instituted as soon as possible after the accident. If these measures fail to bring about a satisfactory reestablishment of the arterial circulation within one to four hours removal of the embolus by arteriotomy should then be performed. Heparinization of the patient immediately after the operation insures against the reformation of blood clots at the site of the arteriotomy wound.

INTRAVASCULAR INJURIES TO UPPER ARTERIES

The importance of controlling hemorrhage from accidental or operative wounds of major arteries is of great concern to the surgeon not only because of the immediate loss of blood which may take place but also because an ample supply of blood to the parts beyond the point of injury must be maintained or serious complications are certain to follow.

Knowledge of the behavior of the peripheral circulation in the extremities or in the brain after the main nutrient artery to that part has been occluded is of paramount importance. It is the duty of every surgeon who deals with vascular disorders to ascertain what alterations in the efficiency of the peripheral circulation will take place if the major arterial trunk of that part is damaged or otherwise interfered with during any surgical operation.

Primary Hemorrhage—If bleeding is external it should be controlled as quickly as possible. Clipping the bleeding point with a hemostat is acceptable except in those cases in which it is desirable to restore the function of the artery. The use of gelatin sponges as advocated by Jenkins and Janda¹ is valuable for controlling hemorrhage from wounds in large blood vessels. If the acute hemorrhage is not readily controllable by direct pressure over the bleeding point the surgeon may resort to the use of indirect pressure—that is, compression of the main trunk of the artery from which the bleeding artery arises. With vertical elevation of the extremity and mild direct pressure in the wound bleeding from almost any peripheral artery can be controlled until preparations for permanent hemostasis can be made. In most instances it is

When a large artery is ruptured by violence its concomitant vein is usually injured also consequently if the individual survives and if the ruptured vessels are not repaired or occluded an arteriovenous fistula may become established. If only the major artery is injured and this artery is covered by a layer of heavy fascia a hematoma is rapidly formed beneath this aponeurosis. Bleeding into this area will continue until the pressure within the hematoma is equal to the arterial pressure.

If the hematoma is not decompressed by surgical operation it may become so tense that the pressure will block the collateral arterial pathways and gangrene of some distal portions of the extremity will ensue. If the pressure on the collateral arterial pathways is not too great to cause gangrene however, the mass of extravasated blood will become organized at the periphery while the center of the mass remains liquid. The mass then develops expansile pulsation. This pulsating hematoma comes to resemble a true arterial aneurysm with the characteristic systolic bruit and thrill in contrast to the arteriovenous aneurysm in which these signs are accentuated in the systolic phase of the heart action but are also continued through diastole.

Dissecting hematomas or aneurysms may cause pressure upon nerves and give rise to severe pain or motor paralysis. They may even erode bony structures like the ribs and result in fatal hemorrhage into large body cavities. This type of complication is illustrated by the following case history.

CASE 2—The patient was a 45 year old white housewife who fell down three steps and sustained a fracture of the proximal end of the left humerus on Feb. 9, 1946. She was taken to a local hospital and a cast applied but the reduction was unsatisfactory. Consequently four days later Steinmann pins were inserted in an attempt to fix the proximal fragment and help reduce the fracture. She was discharged from the hospital one week later. Convalescence was normal for the first three weeks but then she began to complain of burning pain in the left shoulder and left upper chest. The pain became more severe and three weeks later she coughed up some bloodstained sputum. One week after this episode she had the first gross hemoptysis. Physical examination at that time revealed the typical signs of a dissecting aneurysm of the subclavian artery (Fig. 2-4). This continued to increase in size and finally ruptured into the left pleural space causing immediate death (Fig. 5, B).

Arterial Thrombosis—When a major artery is merely contused and the coats of the artery are not ruptured the damage to the intima may be sufficient to cause local intravascular clotting of the blood. If this clotting of blood is progressive it may quickly reduce the efficiency of the collateral arterial circulation by actual extension into the collateral arteries. The immediate use of heparin will effectively control the progression of the intravascular clot but it will not affect the thrombosis which has already taken place.

Leriche² believed that a thrombosed artery is actually a diseased sympathetic nerve and the extirpation of the thrombosed part by arteriectomy removes the factor which is irritating the sympathetic nerves and thus overcomes the reflex vasoconstriction distal to the site of thrombosis. Practical experience has substantiated this concept.

We have found that it is important to use removable aluminum bands when it is necessary to occlude completely the common carotid artery. Such



Fig 1—Rupture of popliteal artery by a bone screw. A Note tips of screws extending through shaft of femur into popliteal space. B Arrow points to end of popliteal artery. Position of bone screw was in relation to the knee. Note numbness of the toes and gangrene of the skin on dorsum of ankle.



Fig 2—Dissecting aneurysm of the subclavian artery. Steinmann pins used to immobilize head of humerus to facilitate reduction of the fracture were inserted too far. The subclavian artery was injured. Note elevation of arm by the dissecting aneurysm.

during surgical operations. When a major artery and its concomitant vein are to be ligated as would be necessary in performing an amputation of an extremity it is extremely important to ligate them separately.

When the ligature includes both the artery and vein in abnormal arterio-venous fistula may develop as the vessel walls beneath the ligature undergo the usual process of necrosis and replacement with fibrous tissue. The development of such an abnormal arteriovenous communication in an amputation stump frequently results in serious cardiac complications.



FIG. 3—Aneurysm in the radial artery following an injury to the wrist. The aneurysm was cured by complete excision with ligation of proximal and distal ends of the radial artery.



FIG. 4—Arteriovenous aneurysm in the broad ligament of the uterus. This result from injury to artery and vein during an operation twelve years previously. The aneurysm was cured by supracervical hysterectomy.

The accidental injury of the ovarian artery and vein or the uterine artery and vein by a vessel or a suture during surgical operations in the pelvis may give rise to arteriovenous aneurysms in the broad ligament. The following case history illustrates this type of complication.

CASE 5—The patient, a 45-year-old white woman, was admitted to the hospital on May 1, 1941. Twelve years prior to this admission she had an incomplete hysterectomy, bilateral oophorectomy and right oophorectomy. Ever since that operation she had had pain in the left lower quadrant of the abdomen. She had a hysterectomy with the freeing of adhesions which afforded no relief. The pain was described as a "cyclical

bands may be removed if the patient shows signs of cerebral ischemia during the immediate postoperative period and no permanent damage of the common carotid artery will result. An illustrative case of progressive arterial thrombosis is as follows:

CASE 3—The patient was a 60-year-old white woman who was admitted to the hospital with an eight-day history of severe pain in the left eye, left side of the forehead and left occipital region. For two days she had been unable to raise the left upper eyelid. On physical examination she was found to have a mild arterial hypertension and a third cranial nerve palsy. An arteriogram revealed an aneurysm of the internal carotid artery just before the bifurcation into the anterior and middle cerebral arteries. That same day an operation under local anesthesia the internal and external carotid arteries were occluded simultaneously for thirty minutes with no untoward effect. The common carotid artery and external carotid artery were then ligated with umbilical tape. The immediate postoperative condition was good but within three hours signs of cerebral ischemia became apparent. The common carotid artery had been permanently occluded by a ligature so that removal of the ligature at that time would not have restored the arterial continuity. At autopsy progressive thrombosis is originating at the site of the ligature and extending into the branches of the circle of Willis was found. If a removable aluminum band had been used this complication might have been avoided.

Arterial Aneurysms—The development of an aneurysm following injury to large arteries may take various forms. This depends on whether a segment of the arterial wall gives way or whether some small spot in the wall weakens. The diffuse weakening of the wall gives rise to the *fusiform aneurysm* while a weakening of one spot in an artery causes the formation of a *saccular aneurysm*. The fusiform aneurysm may rupture at one place and assume the physical appearance of a saccular aneurysm. Such physical alterations must be kept in mind by the surgeon who plans the operative procedure for the cure of an *arterial aneurysm*.

The speed with which arterial aneurysms develop depends upon the extent of the damage to the outer coats of the artery. Penetrating wounds of arteries by sharp objects may cause the rapid development of a pulsating hematoma which quickly assumes the characteristics of a saccular aneurysm and should be treated as one. An illustration of such a complication to an arterial injury is presented by the following case history:

CASE 4—The patient was a 16-year-old white boy who had received a small laceration in the skin of the right forearm. The wound was sutured and the patient was discharged one week later. The wound continued to leave a scar.

The efficiency of the arterial circulation in the hand remains intact in spite of the ligation of the proximal and distal ends of the radial artery.

Saccular aneurysms may remain relatively small for many years after the original injury and then suddenly, because of further trauma or some abnormal strain, start to enlarge rapidly and produce symptoms due to pressure upon surrounding structures.

Arteriovenous Aneurysms—The complication of arteriovenous aneurysms usually occurs when a major artery and its concomitant vein are injured simultaneously. They may also result from improper handling of major blood vessels.

THE CORTICOADRENAL FACTOR IN HYPERTENSION

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INTRODUCTION

THERE are several reasons why an investigation of the corticoadrenal function in human essential hypertension seems of interest. They can be briefly summarized as follows:

1 Experimental renal hypertension produced by the Goldblatt clamp is greatly diminished or disappears after bilateral adrenalectomy in dogs whose life is maintained by cortical extracts.¹⁻⁴ Whether this is due to a specific action of the cortex on renal hypertension or due to the general changes produced by adrenalectomy is uncertain but it seems that in adrenal insufficiency there is a reduction of sensitivity to the pressor effect of renin.^{5,6,7,8} This has been explained by the fall in concentration of hypertensinogen in the blood^{4,9} which returns to normal on administration of cortical extracts or desoxycorticosterone.

2 According to the concept of Selye¹⁰ hypertension is an expression of the "general adaptation syndrome." In his animal experiments corticoadrenal stress as manifested by storage and elimination of cortical lipids and decrease in the lymphocytes in the blood is an essential part of the "alarm reaction."^{11,12}

3 Epinephrine infusion or splenic nerve stimulation may cause an increased corticoadrenal secretion. Splenic nerve section, however, does not interfere with the basic corticoadrenal output.¹³ This effect is demonstrated by the decrease of the cholesterol and ascorbic acid content of the gland, but mediated through anterior pituitary action.¹⁴

4 In man some authors believe that the incidence of hyperplasia or adenomatous change in the adrenal glands of hypertensives is higher than in the control group.^{15,16} This is denied by others.^{17,18}

5 The full blown Cushing's syndrome shows a plasma electrolyte disturbance which is diametrically opposed to that seen in Addison's disease.^{19,20} Experimentally the overactivity of the eosinophil cells of the anterior pituitary gland which are trophic to adrenal cortex produce diastolic hypertension no matter how this eosinophil preponderance is produced.²¹

6 In a hypertensive patient a subsequently developing Addison's disease produced a normal blood pressure as long as the patient was kept on salt alone. When desoxycorticosterone was administered the elevation of blood pressure returned.²² When normal individuals are subjected to a sudden withdrawal of sodium they lose water weight and go into a syndrome characterized by increased sweating, anorexia and extreme weakness,²³ but in essential hypertension this does not happen. The patients lose minimal weight

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arche, was becoming more and more severe and had spread into the left flank. The classical signs and symptoms of an abnormal arteriovenous communication in the pelvis were present. At operation an arteriovenous aneurysm in the left broad ligament was found (Fig. 4).

In general any operation which does not actually close the arteriovenous fistula must be considered undesirable and when such operations are performed there is danger of not only failing to cure the aneurysm but of causing serious circulatory disturbances distal to the arteriovenous fistula. Gangrene may develop as a result of ligation of the artery proximal to the arteriovenous aneurysm because the shunt or spillway remains open and there is no longer enough arterial force to push the blood beyond the fistula.

The most insidious and perhaps the most serious of the complications which may follow the establishment of arteriovenous fistulas following trauma to large blood vessels is the marked hypertrophy and dilatation of the heart with subsequent myocardial failure. These changes are usually late effects but cardiac decompensation has been observed within five days after the establishment of the arteriovenous communication.⁴ It must therefore be borne in mind that it may be necessary to subject the patient to operation much earlier than ordinarily would be the case because of this cardiac complication. One method of temporarily relieving the strain on the heart under such conditions consists in ligation of the vein some distance proximal to the arteriovenous communication.

SUMMARY

We have presented a review of some of the complications which may follow various types of injuries to major arteries and their concomitant veins. We believe that a thorough understanding of such complications will enable surgeons to reduce the number of catastrophes which all too frequently nullify their most conscientious efforts. Lord and Pruddenbach⁵ have emphasized the importance of having the operating room of every hospital properly equipped to care for all types of injuries to the major arteries and they suggest that properly trained surgeons should be available at all times to handle such injuries. We agree that a determined effort should be made to teach young surgeons the important factors in the management of injuries to large blood vessels and then they should be provided with facilities which will permit proper care of such injuries. The progress of this important field of surgery will depend greatly upon the success and the thoroughness of such an educational program.

REFERENCES

1. Jenkins, Huber and Janis Rudolph. Studies on the Use of Gelatin Sponge or Form as an Hemostatic Agent in Experimental Liver Resections and Injuries to Large Veins. *Ann Surg* 121: 1, 959 1946.
2. Leriche, Rene. *Physiologie pathologique et Chirurgie des Artères*. Paris 1947. Masson & Cie.
3. Herrmann, Louis G. and Reil, Mont R. The Surgery of Large Arteries. Bancroft's Surgical Therapeutics Philadelphia, 1947. J. B. Lippincott Company.
4. Mason, J. M. Extreme Cardiac Decompensation Following Traumatic Arteriovenous Fistula of the Left Subclavian Vessels. *Am J Surg* 20: 401 1937.
5. Lord, J. and Breidenbach, I. The Management of Acute Traumatic Arterial Emergencies. *S Clin North Amer* 28: 313 1948.
6. Herrmann, Louis G. The Management of Injuries to Large Blood Vessels in Wounds of Violence. *Am J Surg* 74: 560 565 1947.

some of the typical responses to this dose of insulin in hypertensive individuals (Fig 1). It will be noted that some curves showed a good response at thirty minutes, with rapid recovery of the blood sugar level in one to two hours, another curve shows a delayed response which does not appear until one hour after injection, and one curve shows a complete resistance to this dose of insulin. Curves may also show a normal dip but a failure of normal return to the fasting level of blood sugar. A recent refinement of insulin

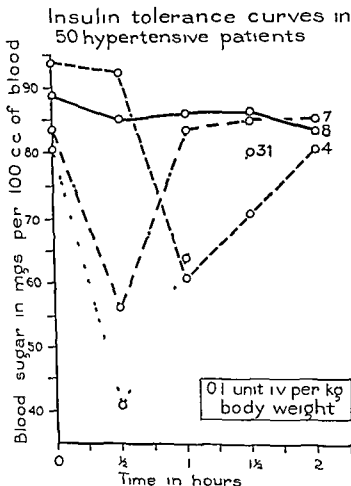


Fig 1—Insulin tolerance curves on fifty consecutive hypertensive patients. Note that thirty-one show a normal response, four show a delayed response, and eight show no response at all.

tolerance test studies the rate of fall in reducing substances in taking samples at short intervals especially at ten and twenty minutes. A delay in the fall was observed in malignant hypertension and acromegaly.

Insulin tolerance curves were determined on 50 consecutive hypertensive patients during their preoperative study. Of these, 31 showed a normal response, 4 showed a delayed response, 7 showed an early dip and returned

and are asymptomatic. This may be due to renal changes or the changes in the kidney mediated by adrenal cortex.²⁴ The low sodium diet or the low protein rice diet may well act through the adrenal cortex.²⁵ Desoxyaceticosterone acetate when administered intravenously acts as a pressor substance in hypertensive individuals.

In previous reports from this clinic^{2, 3} it was pointed out that a small group of juvenile or middle aged hypertensive patients exist who in spite of favorable preoperative studies fail to show a favorable response to the operation; others show a delayed response appearing as late as six months after operation.² For this reason it was decided to study a group of hypertensive patients in regard to their corticoidrenal function.

METHOD OF STUDY

It must be stated immediately with regret that hormonal studies were not within the scope of the laboratory. As a matter of fact the sex hormone production is said to be diminished in hypertension²⁶ and during the general adaptation syndrome the sex hormone production is not stimulated at the expense of sugar active and salt active corticoids.²

The 11 oxysteroids which increase sevenfold on the administration of adrenocorticotrophic hormone²⁷ were not studied. Our methods were so selected that first a simple test was determined for purposes of orientation and when this was found to be positive other methods were used to corroborate the suspicion that adrenocortical hyperfunction might be present.

The Insulin Tolerance—In 1934 Lenn Trump and I²⁸ described a test for insulin sensitivity and summarized the previous literature. Our aim was to distinguish an insulin resistant from an insulin sensitive diabetic patient. A group of factors was listed which were known to increase the action of insulin such as thyroidectomy, hypophysectomy, pancreatectomy, high carbohydrate diet and alkaline diet. To these our animal experiments added celiac ganglionectomy, adrenal denervation and splanchnic nerve section.^{2, 29} One factor which has since then become known mostly through the work of Jensen and Cattin³⁰ is the glycotropic anti-insulin substance of the anterior pituitary gland which requires the presence and functional activity of the adrenal cortex. Humbelot and Rolt³¹ showed that the anti-insulin factor resides in the cosinophil cells of the anterior pituitary gland. It is likely that many of the factors listed in our previous publication act through this mechanism.

Our original test called for an injection of 0.01 unit of insulin per kilogram of body weight given intravenously but since most workers adopted a tenfold dose and since insulin resistance is thus more strikingly demonstrable a dose of 0.1 unit of insulin per kilogram of body weight was used in our present studies.

The test at present consists of the determination of a fasting blood sugar after which insulin is injected intravenously. Blood sugars are determined one half, one, two and three hours after the injection. A graph illustrates

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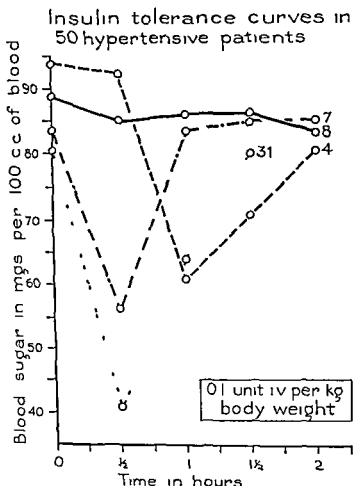


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The Intravenous Sugar Tolerance (Soslin²⁷)—Fuller Albright and his co-workers²⁷ stated that the "sugar hormone" of the adrenal cortex is responsible for the corticoadrenal symptoms of the Cushing's syndrome. For this reason in patients who were suspected of corticoadrenal stress a sugar tolerance curve was obtained. But since the tests were to be repeated after operation and since splanchnic nerve section accelerates upper gastrointestinal motility, it was felt that the intravenous route would eliminate the different rates of absorption from the gastrointestinal tract. The patients were

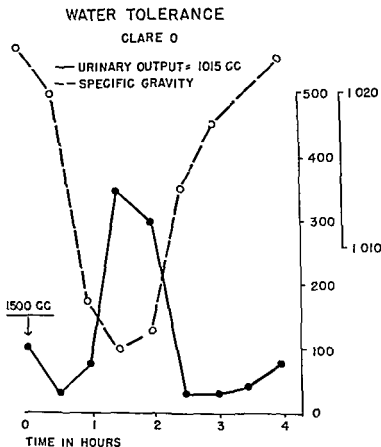


Fig. 2—Water tolerance of a normal individual

given $\frac{1}{2}$ Gm. of dextrose per kilogram of body weight intravenously in 50 per cent solution. Blood sugars were determined before, 30, 60 and 120 minutes after the injection. A normal curve is shown in Fig. 2 together with two abnormal curves (Case 3). Case 2 showed a complete insulin resistance prior to operation. Three months later the insulin resistance diminished and the patient was sugar free on a liberal diet without insulin.

Desoxycorticosterone acetate which has a definite pressor effect in hypertensive patients²⁸ showed no effect on the intravenous sugar tolerance. It

faster than usual to normal, and 8 showed no response at all. Obviously, another possible curve exists namely, a poor response to the insulin hypoglycemia by failing to rise from the initial dip.¹⁷ Such curves are seen in Simmonds' pituitary cachexia and in Addison's disease. Interestingly enough patients who show a great deal of fatigue and listlessness after operation may present such a slow rise following the hypoglycemic dip. Their convalescence may be greatly hastened by cortical extract.

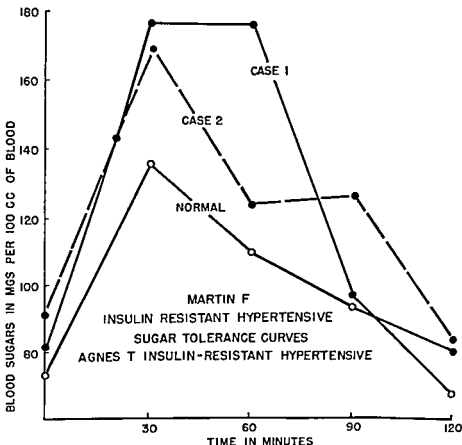


Fig. —Intavenous sugar tolerance curves. Graph illustrates a normal sugar tolerance curve and three curves according to the method of Hoskins.¹⁸ Two other curves illustrate sugar tolerance curves of two patients (Case 1 and Case 2) both of which show insulin resistance.

The eight patients exhibiting insulin resistance were of particular interest. If their insulin resistance was really due to an increased pituitary corticoadrenal activity, what other tests could be used to confirm this assumption and what was their postoperative course? The following additional tests were done in the insulin resistant group of hypertensive patients.

The Intravenous Sugar Tolerance (Soskin¹¹)—Fuller Albright and his co workers¹² stated that the "sugar hormone" of the adrenal cortex is responsible for the corticoadrenal symptoms of the Cushing's syndrome. For this reason in patients who were suspected of corticoadrenal stress a sugar tolerance curve was obtained. But since the tests were to be repeated after operation and since splanchnic nerve section accelerates upper gastrointestinal motility it was felt that the intravenous route would eliminate the different rates of absorption from the gastrointestinal tract. The patients were

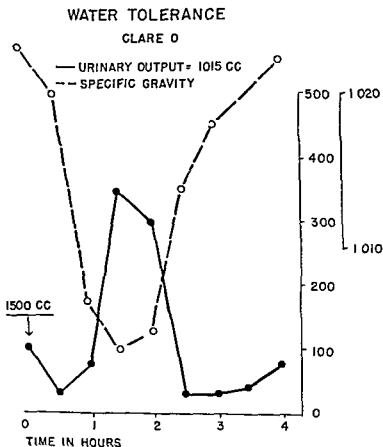


Fig 3—Water tolerance of a normal individual.

given $\frac{1}{2}$ Gm of dextrose per kilogram of body weight intravenously in 50 per cent solution. Blood sugars were determined before, 30, 60 and 120 minutes after the injection. A normal curve is shown in Fig 2 together with two abnormal curves (Case 3). Case 2 showed a complete insulin resistance prior to operation. Three months later the insulin resistance diminished and the patient was sugar free on a liberal diet without insulin.

Desoxycorticosterone acetate which has a definite pressor effect in hypertensive patients¹³ showed no effect on the intravenous sugar tolerance. It

is obvious that this synthesized product is by no means equivalent to the full activity of the adrenal cortex, besides the salt hormone should not affect sugar tolerance

The Water Tolerance—Fasting subjects were given 1500 cc of water to drink in twenty to thirty minutes after being deprived of water and food for fourteen hours. The bladder is emptied just before and every thirty minutes after the ingestion of water for four hours. Volume and specific gravity are determined in the individual specimen

This is essentially the second half of the well known concentration dilution test except that the volume and specific gravity are followed in half hour samples. Normal subjects eliminate 1200 to 1500 cc of urine the specific gravity fluctuates inversely with the output (Fig 3)

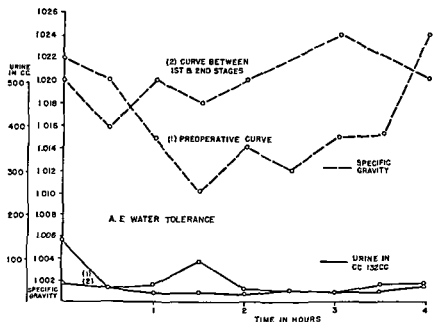


Fig 4—Water tolerance of patient (Ca 3) with a cortical adenoma proved at operation. Note fixed high level of specific gravity and low individual specimens of urine.

It was originally thought that this test would give a measure of salt and water retention and thus relate to the salt water hormone of the adrenal cortex. Truly enough this is illustrated in one patient (Case 3 Fig 4) who was not only partially insulin resistant but who had a large corticoadrenal adenoma removed during the second stage of splanchnic nerve section (Fig 5). It became obvious however that in the average hypertensive patient without corticoadrenal involvement this is an excellent renal function test and that patients can be readily grouped in six patterns.

In another communication² these patterns were described in detail their value lies in establishing a type of renal impairment which seems un-

influenced by splanchnic nerve section and thus is significant in predicting a poor result. Whether the pattern shown in Fig. 4 is typical of corticoadrenal hyperfunction needs to be investigated.

Other Tests—Trials were made with the salt tolerance test of Soffer⁴⁰ with the uric acid creatinine ratio of Thorn³⁹ and the NaCl ratio of Schve⁴¹. Either they were not simple enough for our purpose or there is as yet insufficient experience to evaluate their significance.



Fig. 5—Cortical adenoma removed at operation.

DISCUSSION

In a previous paper⁸ we have offered a diagram of factors which are known to affect directly or indirectly arteriolar tone. In this report the corticoadrenal factor has been studied. Limited experience with the simple clinical tests of insulin, sugar and water tolerance would indicate that a group of patients (16 per cent in the small series of fifty) have shown corticoadrenal hyperactivity interestingly enough if this is due to simple hyperfunction. Splanchnic nerve section gradually over a period from three to six months diminishes this activity. That the adrenal cortex is influenced by sympathetic activity has been suggested by some of our early histologic studies with Cuthbert²² and recently persuasively proposed by Vogt¹³ and by Long.¹⁴ There still remains of course the hormonal action of the eosinophil cells of the anterior pituitary gland on the adrenal cortex and also the autonomous activity of a corticoadrenal adenoma.

From a practical standpoint the use of the simple insulin tolerance is suggestive of corticoadrenal hyperfunction. In such hypertensive patients one

may find corticoadrenal adenoma or a simple hypertrophy. Whether a bilateral partial resection of the adrenal gland should be done as advocated years ago by De Courey,⁴² or whether splanchnic nerve section per se will bring about a slow involution is yet to be determined. At any rate, we now have simple methods at our command to investigate this factor.

There has been no correlation as yet between the insulin resistant patients and those patients who respond to sodium restriction, but it is possible that this would be a simple way to select hypertensive patients for such diet if it could be shown that sodium restriction acts through dampening the corticoadrenal factor as suggested by Grollmann and associates.²⁵ Also, the group of hypertensive patients who have not responded well to splanchnic nerve section and yet do not show extensive adrenal damage may well be benefited by such a procedure.

Attention should be called to the water tolerance of hypertensive patients which seems to have prognostic value as to results from the operation. It is obvious that the corticoadrenal factor, the posterior pituitary factor which has not been discussed here and the renal factor are all at play, however, certain curves are so suggestive of late nephrosclerosis that together with the results of other renal function tests they form a contraindication to operation.

SUMMARY

There are experimental data and clinical observations recorded in the literature which suggest that corticoadrenal activity is a factor at least in some cases of hypertension. In this preliminary study the significance of insulin tolerance, sugar tolerance and water tolerance has been discussed. Insulin resistance means an activity of pituitary eosinophils mediated through the adrenal cortex. The sugar tolerance in corticoadrenal stress seems to be diminished just as in acromegaly. The water tolerance dependent on a number of factors is a sensitive index of renal function and has prognostic value as to the expected results from splanchnic section.

CASE REPORTS

CASE 1 (St. Luke's Hospital No. 94,061) — A T was admitted to the urologic service on June 12, 1947, complaining of headache, vertigo, and dyspnea on exertion. A diagnosis of chronic glomerulonephritis was made in a local community hospital. This 45-year-old patient had a long history of renal disease. Twenty-five years previously she had eclampsia with her first pregnancy and was unconscious for four days. The second and third pregnancies were uneventful. Eleven days after her fourth delivery however she suffered a cerebrovascular accident and was completely paralyzed on the right side. Since this time the patient has been aware of having hypertension, being told that it reached the 200 mm. of mercury level. One week prior to entrance the left side became numb and this prompted the patient's entrance to St. Luke's Hospital. After a urologic survey which was negative she was transferred to our service for management.

On admission the patient's blood pressure was 140/110 mm. of mercury with a regular heart rate of 90 beats per minute. The eye ground revealed a type II hypertensive fundus with a left-sided optic atrophy. She had been blind in the left eye since the age of thirteen years with a sudden onset of unknown cause. The heart occupied 52 per cent of the thorax and the great vessels indicated some widening. The cardiogram revealed myocardial pathology on a hypertensive basis. T was inverted in Leads I and 6F and depressed

in II, and there was left axis deviation. Single specimens of urine revealed no pathology in elements. She was unable to concentrate above 1.013, but diluted to 1.002 specific gravity. The fifteen minute phenolsulfonphthalein test revealed 20 per cent excretion of the dye and the urea clearance was 89.58. A water tolerance revealed that she excreted 869 cc of urine after ingesting 1,500 cc and reconcentrated the urine from an initial level of 1.019 to 1.009 at the end of four hours. The insulin tolerance revealed a completely flat curve (89, 85, 86, 86, and 84 mg per cent). A repetition of this test revealed again this resistance to insulin (103, 94, 96, 86, and 87). The sugar tolerance ($\frac{1}{3}$ Gm of dextrose per kilogram of body weight given intravenously) gave a fasting blood sugar of 81 mg per cent with values of 177, 177, 97 and 67 mg per cent at half hour intervals. Blood chemistry was within normal limits. The blood count was normal, including 12.6 Gm. of hemoglobin per 100 cc of blood.

The medical consultant found moderate enlargement of the heart to the left. The reflexes were active but within physiological limits. The patient showed a fair drop of blood pressure after 9 grains of Sodium Amytal, from 190/120 to 140/100 mm of mercury. On hyperventilation together with pressure on the carotid sinus the blood pressure was lowered to 166/104 mm of mercury. On administration of Pitman (43 cc intravenously) the blood pressure fell from 230/120 to 176/91 in one minute and returned to the original level in six minutes.

This patient was judged suitable for splanchnic nerve section. Of unusual interest was the abnormal water and insulin tolerance. For this reason the adrenals were specifically investigated at operation by completely freeing and inspecting them.

Operations—The two stages of dorsolumbar sympathectomy were performed on June 20, 1947 and July 11, 1947. On both sides the major splanchnic nerve was removed from the midthoracic level to its entrance in the celiac ganglion and the ganglionated chain was removed from above the eighth dorsal to below the second lumbar ganglia. A biopsy was taken from the right renal cortex which showed a slight nephrosclerosis. The adrenal gland on the right seemed normal. The left adrenal, however, seemed larger than usual, somewhat firm and nodular. Since the pressure at this stage of operation was very low and unstable it was felt advisable not to disturb it until the failure of the bilateral sympathectomy should be demonstrated.

The patient's surgical convalescence was uneventful. Because of the preoperative findings and the possible enlargement of the left adrenal, the salt tolerance of Soffer was run in the postoperative period. Without the desoxycorticosterone acetate the patient excreted 30 per cent of the ingested chloride ions whereas after the drug, she excreted 53 per cent, indicating a normal response to the drug. On discharge the blood pressure was 160/80 mm of mercury.

Postoperative Course—The patient was reexamined on October 18, a little over three months following the second stage of dorsolumbar sympathectomy. The cardiogram and two meter chest film showed definite improvement. She had lost twenty pounds and aside from some residual soreness in the back felt very well. She had started to do her own house work. The blood pressure however was 160/115 mm of mercury, an improvement over the preoperative reading. Insulin tolerance was 91.5, 57, 72 and 81 mg per cent, which now fell within normal limits.

Comment—This case history indicates a type of hypertension which manifests insulin resistance or other evidence of corticoadrenal activity such as a tendency to salt and water retention and hyperproteinemia which are suggestive of corticoadrenal hyperfunction. It is most interesting that this patient although not showing a change in insulin response immediately after the operation exhibited a normal insulin response three months after operation together with a marked clinical improvement. The improvement, however, was temporary and nine months after operation, while asymptomatic,

she returned to the hospital with blood pressure at the preoperative level. At this time, the left adrenal gland was re explored and found to be normal and an uncut left lumbar chain was resected. This resulted in a fall of blood pressure to 160/100 mm. of mercury. The insulin and water tolerance were now within normal limits and the sugar tolerance was now quite normal. The last examination eleven months after the operation showed the blood pressure to be varying between 180 and 174 systolic, 110 and 108 diastolic pressure. This is a good result considering the amount of organic vascular damage.

CASE 2 (St Luke's Hospital No 1030,2)—M F a 41 year old manufacturer entered St Luke's Hospital with a hypertension of six years duration. In 1941 his family physician discovered diabetes and hypertension on examining him for severe headaches and weight loss. The blood pressure fluctuated a great deal and varied between 200 and 160 mm. of mercury. A year before admission severe substernal ache appeared on exercise. Treatment consisted of rest, relatives, and nitroglycerin. He was placed on a weighed diet with 20 units of protamine zinc insulin. Later dyspnea developed on very little exertion and vision became blurred in spite of newly fitted glasses. The patient's father died of coronary occlusion at the age of 74 and his mother died of cancer at the age of 60.

On admission the patient's blood pressure was 210/136 mm. of mercury on the left arm. He showed some evidence of cardiac decompensation. The eye grounds showed marked sclerosis of the arterioles and several white dots indicating previous hemorrhage but no cotton wool exudates. The heart was slightly enlarged to the left, but its rate was regular and there were no murmurs. The cardiogram revealed sinus rhythm and left axis deviation. On the two meter chest film the cardiothoracic ratio was 43 per cent and there was considerable vascular engorgement. The brachial metabolic rate was -6 per cent. Blood chemistry revealed a blood sugar of 112 mg. per cent and a blood cholesterol of 365 mg. per cent on the preoperative diabetic management. The urea nitrogen was 16.0 nonprotein nitrogen 40 mg. per cent. He concentrated urine to 1000 and diluted to 1000; the phenolsulfonphthalein test showed 40 per cent excretion in one half hour and the urea clearance was 52.93 cc. per 100 cc. of blood. Total protein was 8.12 with 2.00 albumin and 6.12 globulin.

Four insulin tolerance curves were determined: one before, one after the first stage of parathyroidectomy and two after both stages were completed. The four curves are given in Table I.

TABLE I

	112	80	74	91	90
1 Preoperative curve	112	80	74	91	90
2 After first operation	114	114	116	117	114
3 After second operation	114	10	10	110	111
4 Five months after second operation	110	13	64	81	116

Since he weighed 200 pound the insulin given was 9 units intravenously which failed to produce an appreciable drop in the blood sugar levels. Vasomotor tests revealed the following: Ice water raised the blood pressure from 190/110 to 196/144 mm. of mercury. On exercise the pressure rose from 196/144 to 239/130 mm. of mercury. On Flamon the lowest pressure obtained was 160/114 mm. and on Sodium Amytal the lowest pressure obtained was 160/100 mm. of mercury.

Sympathectomy was advised for two reasons: First to stabilize the diastolic pressure around 110 mm. of mercury if possible and, second to improve the insulin resistance and thus perhaps the diabetes.

Operations—Operations were done on November 7 and December 3, 1947. Both stages were followed by some atelectasis and considerable intercostal neuritis but he left the hospital in good condition on December 17, with no digitalis or insulin with a diet of protein 160,

fat 70 carbohydrates 90, and a blood pressure of 154/100 mm of mercury lying down, which fell to 60/0 mm of mercury on standing

Postoperative Course—For some time the patient complained of much abdominal tenderness and required narcotics. He ate poorly. A roentgenologic study of the gastrointestinal tract was negative. Gall bladder visualization revealed a well functioning gall bladder. The blood pressure was 160/100 in bed, on standing it fell to 100/60 mm of mercury. Two months after operation the patient for the first time showed some response to insulin. The blood pressure was 160/100 mm of mercury and he had started working again. He showed considerable improvement and had a fasting blood sugar of 117 mg on the preoperative diet without insulin. Five months after operation the insulin tolerance was 120, 73, 64, 81, 116 mg per 100 cc of blood. The blood pressure was 160/100 mm of mercury lying down and 138/90 mm on standing. The result persists to date (June 15 1949).

CASE 3—A J E, a 33 year old production manager was first admitted to St Luke Hospital on September 14 1947. He had known of hypertension for ten years, at which time the blood pressure was 160 mm of mercury. Five years before admission the systolic pressure was said to be 200 mm of mercury. Three months before admission he had a right sided apoplexy which left him with some residual spasticity in the hand with difficulty in writing. He complained of no headaches, dizzy spells, chest pain, or edema.

On admission the blood pressure was found to be 212/130 mm of mercury. Reflexes on the right were exaggerated. The eye grounds showed grade II retinopathy. The heart and aorta showed moderate enlargement. The cardiogram revealed myocardial pathology of a hypertensive type. The urea nitrogen was 23.9 mg per cent, the nonprotein nitrogen, 4 mg per cent giving a urea ratio of 50. Other values of blood chemistry including sugar, cholesterol and total protein were within normal limits. The urine showed no pathological elements. The water tolerance revealed a curve suggestive of corticoadrenal activity of the salt factor (Fig 4). The fifteen minute phenol sulfonphthalein excretion was 25 per cent, the urea 40.49 cc per 100 cc of blood. The intravenous pyelogram was normal. The insulin tolerance showed a diminished response starting with a fasting blood sugar of 84 mg per cent, a maximal dip to 56 mg per cent at half an hour followed by blood sugar of 75, 80 and 81 mg per cent at half hour intervals, an abnormal curve. Fasting metabolism was +1 per cent. The cold pressor test raised the blood pressure to a ceiling of 240/160 mm of mercury whereas the sodium amyl test lowered it to a minimum of 110/90 mm of mercury. Because of the marked variability of the blood pressure and comparatively little organic damage with the exception of the cerebrovascular accident operation was advised. The significance of the water tolerance and insulin tolerance was not fully appreciated.

Operations—A two stage plancinic nerve section and lumbar dorsal sympathectomy were performed. Renal biopsy from the right side revealed nephroclerosis and chronic interstitial inflammatory foci in the kidney. Between the two stages the water tolerance test was repeated and showed a pattern identical with the first one. The blood pressure was 224/130 mm of mercury a month after the first stage and the patient suffered from intercostal neuralgia. At the second stage a large cystic adenoma of the left adrenal gland was found and was removed with the adrenal gland from which it could not be separated.

Postoperative Course—The patient's blood pressure was 150/100 on discharge. The water tolerance now showed a good dilution and reconcentration in four hours. The insulin tolerance on May 16, 1948 ten weeks after removal of the cortical adenoma and bilateral splanchnic nerve section, was 110, 51, 68 and 79 mg per cent, showing a return to normal. The blood pressure now is 140/110 with the patient lying down and 134/100 standing.

CASE 4—H F, a 23 year old housewife was admitted to St Luke Hospital on May 1948 complaining of nervousness for six years, severe headaches for two years, a stroke one and two years before admission, with transient aphasia and paralysis of left and right upper extremity for four to six weeks each time, coldness of lower extremities and occasional hematuria.

The patient was perfectly well until six years before admission, when she became very nervous. Five years before she had a severe toxemia of pregnancy with convulsions and generalized edema for the entire third trimester. The infant was stillborn. While the patient had scarlet fever at the age of 9 years, which left her with a discharging ear, she had no kidney trouble and the blood pressure was not elevated before the pregnancy. The family history was not contributory.



Fig. 6—Intravenous pyelogram of H. F. (Case 4). Note calcified scattered spot in region of right adrenal gland. Her history together with low blood pressure and marked insulin sensitivity are highly suggestive of adrenal insufficiency.

On admission, the patient's blood pressure was 130/90 mm. of mercury. Physical examination revealed a slight left lumbar tenderness and residual weakness and spasticity of both arms and hands. There was left facial weakness. Eye grounds revealed a slight bitemporal pallor of the discs. The heart occupied 4 per cent of the thorax. Electrocardiogram showed evidence of myocardial damage. She concentrated urine to 162 m. and diluted to 1002. excreted the dye to 20 per cent in fifteen minutes. The urea clearance was 74.4 c.c. (standard). There was persistently more than 50 mg. of albumin in the urine. The intravenous pyelograms were normal, but there were some calcified spots to the right and left of

There was some
be well organized,
of mercury. On
ephine raised the
immersion into ice water the 1st systolic
blood pressure from 130/90 to 100/100 mm. of mercury. The impression was that of a post

eclamptic hypertension resulting in diffuse arteriolar disease. The diastolic pressure was consistently above 90 mm. of mercury, but the systolic was low due to myocardial damage or possibly damage to the adrenal glands.

Operations—Operations were performed on May 20, 1942, and June 8, 1942. Following the first stage the patient exhibited a temperature of 101.6° F., a slow pulse and respiration, and a marked mottled peripheral cyanosis. This was thought to be a cerebral vascular accident in the midbrain or a Waterhouse-Friedrichsen syndrome which fortunately subsided in three days. The second stage was performed nineteen days after the first one without any unusual complication. The kidneys were small and firm and both adrenals were also visualized, while the adrenals felt smaller and more nodular than normal, there was no evidence of tumor or calcification on palpation. The renal biopsy taken from the right kidney showed marked fibroblastic changes, there were wedge-like sections of cellular fibrous tissue which extended deep into the parenchyma. Here the tubules and glomeruli had undergone marked retrogressive changes. There were clusters of atrophic glomeruli reduced to masses of hyaline material and the tubules had disappeared almost completely. There were also lymphocytes with small residues of tubule cells. There were various stages of involution but outside these wedges the tubules contained columnar lining cells and the lumina were filled with granular precipitates. The glomerular tufts in the scarred portions were also cellular and had considerable fibrous stroma. The large blood vessels included in the scarred portions had very narrow lumina and intimal fibrous tissue thickenings, but the blood vessels elsewhere had thick muscular walls with some fibrous thickening along the intimal edge. The interpretation of these findings was that nephrosclerosis was the main tissue change.

Postoperative Course—When the patient left the hospital on August 19, 1942, the blood pressure was 112/86. The epinephrine sensitivity decreased. She was re-examined on July 3, 1943, and found to have a blood pressure of 110/70 lying down and 100/70 in the standing position. She felt well and used the paralyzed arm more freely. Seven years later she still has a normal blood pressure but is anemic.

Comment—This was a frail, constitutionally inferior patient who received a severe vascular lesion during pregnancy. Whether there was a latent adrenal insufficiency present was uncertain and it was not feasible to test her for this at the time. The cerebral, cardiac, and renal lesion might have been embolic in nature, originating from a subacute bacterial endocarditis but this suggestion, made by our medical consultant, could not be confirmed or disproved. While the weakness and easy fatigability persist to this time, the blood pressure has remained normal for seven years and she can do her own housework. The diagnosis of post-eclamptic hypertension is still the most likely. She was readmitted to St. Luke's Hospital five and one half years later for a check up. The insulin tolerance showed an abnormal sensitivity to insulin, the blood sugar being 71, 58, and 28 in one half hour, at which time she had to be given orange juice because of hypoglycemic symptoms. No other test (Kepler-Wilder test or the water tolerance) showed any abnormality. The diagnosis of post-toxicemic vascular damage with mild adrenal cortical insufficiency was maintained.

REFERENCES

1. Coldblatt, M. Studies on Experimental Hypertension. V. The Pathogenesis of Experimental Hypertension Due to Renal Ischemia. *Ann. Int. Med.* 11: 69, 1937.
2. Blalock, A., and Levy, S. L. Studies on the Etiology of Renal Hypertension. *Ann. Surg.* 106: 821, 1937.
3. Collins, D. A., and Wood, F. H. Experimental Renal Hypertension and Adrenalectomy. *Am. J. Physiol.* 123: 2-4, 1938.

- 4 Gaudino A M Las Suprarenales en la Hipertension Arterial nel Rogeno, argent de biol 20 460, 1940
- 5 Williams J R The Relation of the Adrenal Glands, the Action of the Renin Substance Am J M Sc 193 212 1939
- 6 Friedman B Sokolov T and Oppenheimer F F The Relation of Renin to the Adrenal Gland, Am J Physiol 128 481 1940
- 7 Remington J W, Collings S D, Hays H W, Parkers W M and Swingle J The Response of the Adrenalectomized Dog to Renin and Other Pressor Substances Am J Physiol 132 622 1941
- 8 Howes B A and Dexter L The Sensitivity to Hypertension Adrenalectomized and Unanesthetized Normal Adrenalectomized Hypophysectomized and Adrenalectomized Dogs Ann Int Med 17 451 1942
- 9 Lewis H A and Coldblatt H Studies on Experimental Hypertension V. Experimental Observations on the Humoral Mechanism of Hypertension in the Dog York Acad Med 18 459 1942
- 10 Selye H H The General Adaptation Syndrome and the Diseases of Adrenal Insufficiency J Clin Endocrinol 6 117 1946
- 11 Sayers G, Sayers M A, Fry E G, White A and Long C N H The Effect of Adrenotropic Hormone of the Pituitary on the Cholesterol Content of the Liver (man) With a Review of the Literature of Adrenal Cholesterol, Yale J Med 16 761, 1944
- 12 Douglis J C The Adrenal Cortex and Hypertension J Clin Endocrinol 6 117 1946
- 13 Vogt M The Adrenal Cortex and Hypertension J Clin Endocrinol 6 117 1946
- 14 Long C N H The Conditions Associated With the Secretion of Adrenaline Federation Proc 6 461 1947
- 15 Sarason F J Adrenal Cortex in Systemic Disease Arch Int Med 71 7 1947
- 16 Rinehart J F, Williams O D and Caffery W S Adenomatous Hypertension of the Adrenal Cortex Associated with Essential Hypertension Arch Pathol 169 1941
- 17 Bruger M, Loenkranz J A and Loewenstein B F Studies on the Mechanism of Adrenal Cortex and the Excretion of 17 Ketosteroids in Hypertensive J Am J M Sc 208 212 1944
- 18 Deming W S The Adrenal Cortex in Essential Hypertension Arch Pathol 163 1942
- 19 McQuarrie, J, Johnson I M and Ziegler M R Plasma Electrolyte Disturbances in Hypertension J Clin Endocrinol 6 117 1946
- 20 Ande J C The Adrenal Cortex and Hypertension J Clin Endocrinol 6 117 1946
- 21 Hein J C The Adrenal Cortex and Hypertension J Clin Endocrinol 6 117 1946
- 22 Perera G A The Relationship of the Adrenal Cortex to Hypertension in Man With Hypertensive Vascular Disease J A M A 129 53 1947
- 23 Perera G A and Bleif D W Disturbances in Salt and Water Metabolism in Hypertension, Am J Med 1 602 1946
- 24 Perera G A and Bleif D W Free or Active Activity of Desoxycorticosterone Acetate in Normotensive and Hypertensive Subject Ann Int Med 27 401 1947
- 25 Grollmann A, Harris O T P, Mason M F, Baxter J, Crampton J and Reilly F Sodium Retention in the Diet for Hypertension J A M A 129 53 1947
- 26 Grollmann M L and Schroeder H A The Immediate Pre-salt Effect of Desoxycorticosterone Acetate Science 107 2 1948
- 27 De Takats C and Fowler F F The Surgical Treatment of Hypertension I. Neurogenic Versus Renal Hypertension From the Standpoint of Operative Surgery 21 7-3 1947
- 28 De Takats C, Julian O C and Fowler F F The Surgical Treatment of Essential Hypertension IV. Case Selection and Technique as Influencing Results & Results J Clin Endocrinol 6 117 1946
- 29 Poppen J L and Lemmon C The Surgical Treatment of Hypertension J A M A 134 1 1947
- 30 Thorn G W, Irony F T G and Forsham P H Changes in Urinary Steroid Excretion and Correlated Metabolic Effects During Prolonged Administration of Adrenocorticotrophic Hormone in Man Science 105 498 1947

- 31 De Takats, G, Fenn G V, and Trump R A Splanchnic Nerve Section in Juvenile Diabetes I Selection of Cases for Operation Ann Int Med 2 1201, 1934
- 32 De Takats, G, and Cuthbert, F P The Effect of Celiac Ganglionectomy on the Sugar Tolerance of Dogs Am J Physiol 102 614 1932
- 33 De Takats, G and Cuthbert, F I The Effect of Suprarenal Denervation and Splanchnic Nerve Section on the Sugar Tolerance of Dog, Arch Surg 30 151 1935
- 34 Jensen M, and Grattan J Identity of Glycotropic (Anti Insulin) Substance of the Anterior Pituitary Gland Am J Physiol 128 270 1940
- 35 Heinbecker, P, and Rolf D Hypophyseal Eosinophil Cell and Insulin Sensitivity, Am J Physiol 14 56 1944
- 36 Kronenberg, G J, and McCullough W S A Brief Insulin Tolerance Test, Proc Soc Exper Biol & Med 64 49., 1947
- 37 Frazer R Albright, F, and Smith P M The Value of the Glucose Tolerance Test the Insulin Tolerance Test and the Glucose Insulin Tolerance Test in the Diagnosis of Endocrinologic Disorders of Glucose Metabolism J Clin Endocrinol 1 297, 1941
- 38 So kin S and Levine R Carbohydrate Metabolism Correlation of Physiological Technical and Clinical Aspects Chicago, 1946 University of Chicago Press
- 39 De Takats C and Fowler F F The Water Tolerance of Hypertensive Patients Its Relation to Operability Am Heart J (In press)
- 40 Soffer L J Lesnik G Sorkin S Z Sobotka H and Jacobs M The Utilization of Intravenously Injected Salt in Normals and in Patients With Cushing's Syndrome

REVASCULARIZATION OF THE HEART

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THIS paper contains discussion of two points that were not in our recent publication¹. One of these was omitted, the other is new information on the subject. In this paper I shall try to apply comparative values to various aspects of our work on revascularization.

Trigger Mechanism in the Heart—The concept of 'trigger' was a helpful guide in the experimental work. We found that local anoxia in the myocardium destroyed the coordinated contraction of muscle fibers and ventricular fibrillation appeared. Local anoxia was produced by ligation of arteries to an area of myocardium. As these small coronary arteries were ligated one after another usually four or five of them, the area of myocardium supplied by these vessels became cyanotic and then a sudden fibrillation appeared. There seemed to be an analogy between this mechanism in the heart and a similar mechanism in the brain. Focal anoxia in the brain produces a convulsion of skeletal muscle, focal anoxia in the heart produces a convulsion of heart muscles. The one does not produce death, the other produces death.

We formed an opinion that generalized anoxia of the heart muscle was better tolerated than localized anoxia of myocardium. For purpose of illustration let us assume that it is possible to reduce arterial circulation by 25 c.c. of blood per minute. It appeared to us that this reduction in blood supply would be tolerated better by the heart if the reduction were made at the level of the common left coronary artery than if it were applied to either branch of this artery and that either of the two major branches that is, the descending or the circumflex arteries would tolerate a reduction of 25 c.c. per minute better than if this reduction in flow occurred in the peripheral bed of myocardium. We do not have flow studies to support this belief but such studies in my opinion are not necessary. This idea conforms to laws of the circulation in general. Along this same line of thought is the idea of a marginal blood supply to a potential trigger. This term was used to designate that quantity of blood that held the trigger in abeyance without which ventricular fibrillation occurred. To continue with this line of thought there were then two aspects to the coronary problem. One concerned total flow the other concerned marginal flow. The one concerned continuous function of the heart and when reduced brought about heart failure with the usual signs of dyspnea and edema. The other if

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This work was aided by a research grant from the Division of Surgery U. S. Public Health Service.

In our experimental work we attempted to increase total blood supply (1) by grafting vascularized tissues to the surface of the heart with expectation of blood vessels growing across from the graft to the heart and (2) by converting the coronary sinus into an artery. To equalize distribution of blood so that it could do the heart the most good we attempted (3) to bring about the development of intercoronary channels. These intercoronary channels made it more difficult for "trigger zones" to develop. Communications between coronary arteries were produced by development of inflammation on the surface of the heart. Several thousand dogs were used in the development of this work which was begun in 1932 which was interrupted for three years by the war and which was begun again in 1945 and is in progress at the present time.

Measurements of Benefit—To determine value or effectiveness of any experimental procedure in this work we ligated the descending ramus of the left coronary artery at its origin in one step and then determined results. Mortality rate and in dogs that survived the ligation the amount of destruction in heart muscle were determined. The results in fifty normal dogs were reported by Stanton, Schlicht and Beck.² Mortality was 70 per cent. In each dog that survived ligation a definite infarct was found. The destruction of heart muscle was always definite and extensive. Never was it possible to ligate this artery in a normal dog without definite destruction of heart muscle. A statement can be made concerning the value or effectiveness of these three methods. In order of importance I would arrange these methods as 2, 3 and 1 with arterialization of the sinus as most effective and extracoronary communications as least effective. In the ten year period before the war Methods 1 and 3 were developed. Method 2 has been developed since the war.

Intercoronary and extracoronary communications together reduced mortality by one half and also reduced the size of the infarct. We had a few specimens in which no infarct was present. Thirty-seven patients with severe coronary artery disease were operated upon using these methods. The clinical results were beneficial. Some of the patients were completely relieved of pain and were able to return to work. The clinical results confirmed the experimental studies.

Arterialization of the Sinus Method 2 (Fig 1)—The historical background of this work has been published and need not be repeated here. We developed an operation whereby arterial blood was delivered to the coronary sinus. This was accomplished in two ways: (1) by anastomosis between common carotid artery and coronary sinus; (2) by a free graft of vein between aorta and coronary sinus. After the technique of the operation was developed so that it could be done successfully the next step was to apply tests or measurements of benefit. We did sixty-seven experimental operations before we were able to make the first successful anastomosis. The development using carotid artery preceded the development of the free graft off the aorta.

Measurements of benefit applied immediately after anastomosis between carotid artery and coronary sinus. In these experiments the left common carotid artery was dissected free in the neck. It was transected and turned down into

the chest. Anastomosis between artery and coronary sinus was made. Immediately after the anastomosis was completed the descending ramus of the left coronary artery was isolated and completely ligated at its origin. Our statistical records in these experiments were not entirely complete because our operative notes of the work two years ago when the experiments were done were largely a record of repeated failures. The approximate number of these experiments was six. There were five deaths and these occurred before closure of the chest was completed. There was one recovery. The heart in this dog showed a large infarct. Conclusion was made that under these experimental conditions arterialization of the sinus was not beneficial. The measurements of results were the same as those obtained in normal control experiments. In 1938 Gregg and Dawald¹ reported results of their studies on the effect of arterial blood delivered to the coronary sinus. In these experiments arterial blood was delivered under pressure into the coronary sinus. These were acute physiologic experiments and in so far as I know, were the first studies on this subject. The conclusion by Gregg and Dawald was that arterial blood delivered to the sinus did not have great value to the heart. The status of our work then at the end of six months of effort was that there was no evidence of benefit by the anastomosis between coronary artery and coronary sinus. We then decided to place an interval of time between anastomosis and test of benefit.

Measurements of benefit applied two weeks after anastomosis between caudal artery and coronary sinus. Ten dogs with patent anastomosis were taken in this series. Two weeks after anastomosis was done the descending ramus of the left coronary artery was completely ligated at its origin in this series. Each dog made an immediate recovery. One died at the end of eight days, one died at the end of thirteen days and eight dogs recovered. In a control group of ten dogs in which the anastomosis was blocked off by thrombus so that no blood passed through the anastomosis, death occurred almost immediately in seven and recovery occurred in three after this artery was ligated. The specimens in both series were examined for destruction of myocardium: ten specimens in the group with patent anastomosis and three specimens in the group with thrombosis. In the series with patent anastomosis there was no infarct in four specimens and in the remaining six the infarct was small. In no specimen was the infarct large and extensive. The three specimens of the control group each showed a large infarct. The infarcts in the two groups are shown in Figs. 2 and 3. These tests of benefit then indicate that arterIALIZATION of the sinus has great benefit to the heart after an interval of time. These results are definitely better than any results obtained in our previous work. It would appear that certain adjustments in the circulation take place after anastomosis and that time is necessary for beneficial effects to manifest themselves. We found that if heparinized blood is injected into the sinus in a retrograde direction 9 c.c. per minute were recovered from the coronary artery in the normal dead heart. Two weeks after ligation of the sinus that figure was increased to 22 c.c. per minute. It would appear that the vascular bed in the heart opens up more freely after ligation of sinus and that adjustments take place after arterial anastomosis to the sinus has been made. These adjustments in the circulation invite further study.

Fig. 1



Fig. 2

Fig. 1—Dog heart. Arteries in red, veins in blue. Note rich vascularization. Communication exists between venous and arterial bed. The communications can open up so that arterial blood introduced into the venous system enters the arterial system where oxygen exchange is possible.

Fig. 2—Dog heart. White vessel at base of heart is carotid artery grafted to coronary sinus. Specimen 4 months after anastomosis. Arteries in red, veins in white. Note communication between coronary sinus system and veins over right ventricle. These veins enter the right auricle. They may drain blood from coronary sinus system into auricle without going through capillary bed of left ventricle. These veins can be ligated.

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Measurements of benefit applied two weeks after anastomosis between carotid artery and coronary sinus. Ten dogs with patent anastomosis were taken in this series. Two weeks after anastomosis was done the descending ramus of the left coronary artery was completely ligated at its origin in this series. Each dog made an immediate recovery. One died at the end of eight days, one died at the end of thirteen days and eight dogs recovered. In a control group of ten dogs in which the anastomosis was blocked off by thrombus so that no blood passed through the anastomosis, death occurred almost immediately in seven and recovery occurred in three after this artery was ligated. The specimens in both series were examined for destruction of myocardium: ten specimens in the group with patent anastomosis and three specimens in the group with thrombosis. In the series with patent anastomosis there was no infarct in four specimens and in the remaining six the infarct was small. In no specimen was the infarct large and extensive. The three specimens of the control group each showed a

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Optimum Amount of Blood to the Sinus—After measurements of benefit were obtained our thoughts turned to application to patients. We had been using the carotid artery in the dog. We decided that the carotid artery probably would not be satisfactory in man. It is larger than the coronary arteries and it is an important artery that cannot always be sacrificed without cerebral complications. There was no other available artery. The subclavian artery presented difficulties in the dissection and to get a sufficiently long segment to reach to the coronary sinus would involve ligation of collateral vessels for the arm. Decision was then made to use a free graft off the aorta. A free graft of artery or vein was used. More recently a graft of jugular vein was used in dogs. The technique of anastomosis was developed. Dogs died one after another after the graft was opened. Death occurred in the first twenty four hours after anastomosis was completed. Frequently it occurred as the operation was



Fig. 2.—Control group of ten dogs. Ligation of descending ramus of left coronary artery at its origin. The mortality was 7 almost immediate in each. Recovery occurred in 3. The destruction of myocardium is shown.

being completed. The dogs that lived until the following day showed signs of heart failure. It was difficult for us to understand why these dogs died. They could tolerate the graft if carotid artery was used. They could not tolerate the graft if a free graft of jugular vein was used. The answer to this problem is simple now but it required several months of work before we proved that the jugular vein delivered too much blood to the heart. We constricted the jugular vein so that its lumen was about 3.5 mm. in diameter and the heart tolerated the graft of vein after it was constricted.

It would appear then that it is possible to deliver too much blood to the heart. This idea is indeed radical departure from established medical thought in reference to coronary artery disease. Many in the past appeared the idea of too little blood to the heart. Never I dare say was it even thought to be possible to deliver too much blood to the heart.



DISCUSSION

In retrospect there were several conditions that could have prevented the development of this work. One was the size of the graft and the amount of blood delivered to the sinus. It was fortunate that we used carotid artery in the early experiments because the amount of blood delivered by the carotid artery was tolerated by the heart. Had we used a graft of jugular vein the heart would not have tolerated the flow. It would have been necessary to constrict the vein in order to get recovery. I do not know whether we would have constricted the vein if we had not known that the carotid artery was tolerated. Another condition that had to be dealt with correctly in order to develop this work concerned the interval of time between anastomosis and ligation of coronary artery for test of benefit. As stated elsewhere, there was no immediate benefit after the anastomosis was opened and an interval of time was necessary in order to obtain beneficial measurements for the operation. This step was essential for the development of the work. A third condition that determined progress was the condition of the virginal sinus. The normal sinus is so delicate that it cannot be sutured in most experiments. After it had been ligated for seven to ten days it became thicker and could be handled more safely at operation. Preliminary ligation of sinus became almost a requirement for success.

Comparative Values Applied to Various Aspects of Arterialization of Sinus—Consideration of *primary* importance. This is the value of arterial blood in the sinus. No other aspect of this subject has equal importance.

Considerations of *secondary* importance.

1 Method by which arterial blood is directed into sinus. We used two methods. Other methods may be developed.

2 Thrombosis. We can usually predict at the time when anastomosis is made whether it will remain patent. We are familiar with the factors that determine thrombosis. We have made approximately fifty patent anastomoses to date.

3 Amount of blood to the sinus. We know that an excessive amount of blood can be delivered to the sinus and no doubt there is an optimum amount. In patients with coronary artery disease one would expect that the amount entering the coronary arteries might be a factor in the optimum flow for the heart through the graft. For the dog with the coronary arteries not occluded we found that the amount delivered by the common carotid artery could be tolerated. We found that the jugular vein off the aorta was not tolerated. We found that if the jugular vein was constricted to about the size of the carotid artery that the heart did tolerate this flow. For the patient with coronary artery disease it would appear to me that the graft should be constricted to about 4 mm in diameter.

4 Arteriovenous fistula. The coronary sinus system of veins has a variable number of communications that flow independently into the right auricle (Fig 4). Will these veins drain off blood so that blood will escape the capillary bed of the left ventricle thus establishing fistulous communications? This possibility exists. We believe that there is an optimum flow to the sinus and that there is a

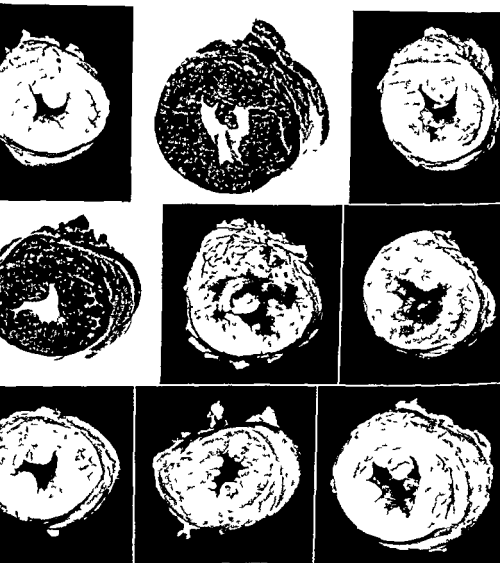


Fig. 3.—Anastomosis between carotid artery and coronary sinus. Two weeks later ligation of descending ramus of left coronary artery at its origin was done in a group of ten dogs. There was no immediate mortality. One died 8 days later, one died 13 days later and eight recovered. Nine of the ten specimens are shown. There is no distention of myocardium in one half the specimens. In no specimen is the destruction extensive as in the control group.

HYPERHIDROSIS

OBSERVATIONS ON THE STUDY OF SIXTY ONE CASES

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HYPERHIDROSIS, or pathologic excessive sweating is part of a symptom complex caused by abnormal stimulation of the sympathetic nervous system. It is usually accompanied by vasoconstriction, and persistence of the condition may lead to certain vascular complications. It is relieved by interruption of the sympathetic pathways. A study of sixty-one cases forms the basis of this report.

The sympathetic nervous system exerts a profound influence, directly or indirectly on all physiologic functions and among these is the control of the peripheral blood vessels and sweat glands. With centers located in the hypothalamus, and possible connections higher up in the brain, sympathetic pathways extend down through the intermediolateral cell column of the spinal cord. From there branches pass out in a segmental manner to the ganglionated chain as white rami and from the ganglia as gray rami to the peripheral nerves. From these nerve fibers are distributed to the blood vessels and sweat glands. They supply both vasodilator and vasoconstrictor fibers to the vessels and the volume blood flow is controlled by stimulating or depressing the impulses. Stimulation of the sympathetics increases sweat secretion while blocking them checks sweating. These responses are so balanced normally that there can be excessive sweating without vasoconstriction and vasoconstriction may occur without sweating, depending on the immediate needs of blood flow and perspiration.

The main functions of sweating is to keep the skin moist and pliable and to aid in the regulation of body temperature, the latter function being controlled by the heat regulation center. Thus a thermal stimulus of increased internal or external temperature brings into action the mechanism for cooling the body and results in generalized cutaneous vasodilatation and increased sweating. A different type of stimulus is that of mental stress brought about by concentration, fear, anxiety, anger and pain which alerts the emergency mechanisms of the body through generalized sympathetic stimulation. The normal response to this stimulus is increased sweating, particularly of the palms and soles, vasoconstriction, tachycardia, rise in blood pressure, increased respirations, and pilomotor activity. In certain types of abnormal stimulation or from increased sensitivity of the sympathetics some of these normal reactions are so exaggerated that a distinct pathologic entity is produced. The observations recorded in the study of sixty-one such cases will be described.

In this group of cases excessive sweating with beads of sweat collecting and dripping off the skin was a constant feature. Vasoconstriction was almost constantly present. Other manifestations such as tachycardia, vasomotor insta-

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ceiling for inflow which should not be exceeded. The inflow will be fixed by constricting ligatures on the graft so that inflow cannot become progressive with time as happens in patients with congenital arteriovenous fistulas. Therefore I assume that this development of drainage channels will reach a maximum and then the development will stop. Perhaps these veins may be beneficial in draining excessive amounts of blood from the venous system. It may be possible to occlude these veins by ligation if they reduce the effectiveness of the new circulation. To my mind the problem of fistulas is of secondary importance. I believe these venous communications can be modified or controlled if necessary.

5 Disease in the aorta. It is possible for disease of the aorta to preclude making anastomosis between aorta and graft. Such cases would be exceptional.

6 Can patients with severe coronary artery disease tolerate the operation? We know that this type of patient is not a good risk for any operation. A number of patients who offered themselves for this operation have died without any operation having been done. As Dr. Gallie recently stated in his presidential address to the American Surgical Association: "Surgeons are engaged in trying to do a large amount of good and a small amount of harm." In reference to patients with coronary artery disease these two factors will have to be balanced one against the other.

Additional considerations might be mentioned and, no doubt, additional problems will appear in the future. Further experimental studies and, at the proper time, application to patients, no doubt, will bring to light additional problems that will need solution. For the present I think we can accept the measurements of arterial blood in the coronary sinus as indicating substantial benefit and with this as a background I feel we should go ahead and try to solve the secondary problems leading to application to patients with coronary artery disease. Up to the present time we have operated upon one patient and we are almost ready to go ahead with application to additional patients.

REFERENCES

- 1 Beck, Claude S., Stanton Eugene, Batiuchok William and Leiter Eugene. Revascularization of Heart by Graft of Systemic Artery Into Coronary Sinus. *J. A. M. A.* 137: 436, 1948.
- 2 Stanton Eugene, Schilit Paul and Beck Claude S. The Effect of Abrasion of the Surface of the Heart Upon Inter-coronary Communications. *Am. Heart J.* 22: 50, 1941.
- 3 Gregg, Donald E. and Dewald Donald. The Immediate Effects of the Occlusion of the Coronary Veins on Collateral Blood Flow in the Coronary Arteries. *Am. J. Physiol.* 124: 435, 1938.

TABLE I CLASSIFICATION OF HYPERSYMPATHOTONIA (PATHOLOGIC HYPERHIDROSIS)
ANALYSIS OF SIXTY-ONE CASES

Primary	Total cases	41
	Female	23
	Male	13
	((general involvement in all cases)	
Secondary		10
A Associated with vascular disease		6
1 Frost bite		
(Bilateral lower extremities, 6)		
Female	2	
Male	4	
2 Frost thrombophlebitis		4
(Single lower extremity 4)		
B Traumatic		4
Bilateral upper extremity	1	
Unilateral upper extremity	2	
Bilateral lower extremity	1	
Female	1	
Male	3	
C Associated with scleroderma		1
Female		
D Post surgical menopause		1
Female		

vertebrae did cause compression of the cord and resulted in permanent paralysis of the lower part of the body. The symptoms of excessive sympathetic stimulation involved only the upper quadrant of the body and probably was a compensatory reaction. This patient developed marked hyperhidrosis of the face, neck and upper extremities. Particularly each day at about the same hour either one or the other side would break out in great beads of sweat. This would last several hours and then dry up and the opposite side would begin to sweat. The other traumatic cases have resulted from milder injuries of the peripheral nerves. In none of these patients were there any signs of disturbed sensory or motor function of the involved nerves yet they presented marked sympathetic stimulation distal to the sites of injury. The patients with associated vascular diseases (secondary group) have all shown varying degrees of inflammation of the vessels in the involved parts. Notably among these have been thrombophlebitis and frostbite. All of these patients have exhibited a strong reaction to vasoconstrictor influences in other parts of the body.

Four of our patients presented localized sweating of a small area of the legs over a chronically inflamed region. Biopsy from one of these showed a diffuse subcutaneous inflammation of the skin and fat pad and a perivascular infiltration of the small vessels. The final two secondary cases were general in character one scleroderma and the other following surgical menopause.

SYMPTOMS

Regardless of the etiology or parts involved hypersympathotonia has certain characteristics. The essential differences between the symptoms of the primary and secondary types are mainly in the extent of involvement. In neither group have the sympathetic ganglia been found organically diseased.

In the primary form the condition may be so mild that for years little attention is paid to it. Then under some new stress and strain it becomes mark-

bility, emotional imbalance and an inner tenseness were often observed, depending on whether or not the sympathetic stimulus was central or peripheral in origin. Adson, Craig, and Brown¹ noted such manifestations in their case reports of hyperhidrosis in 1935. It seems that the term hyperhidrosis, which is only a symptom, is incorrect in classifying this disease. We propose to use the more descriptive term hypersympathotonia for this symptom complex. This implies that through abnormal stimulation normal sympathetic responses are exaggerated to the point of being pathologic in character.

ETIOLOGY

Hypersympathotonia or excessive stimulation of the sympathetic nervous system may occur under a variety of conditions. It may involve the entire sympathetic system or only a portion of it depending on the origin of the stimulus. When the stimulus originates in the brain centers, the hypothalamus having been shown to be the most important, it will affect the entire sympathetic system. It is usually a functional disorder. Rarely does an organic lesion of the brain such as tumor, trauma or inflammatory disease cause hypersympathotonia.

When the exciting stimulus arises from levels below the brain, the cause is usually organic in character. Trauma or inflammatory lesions involving the cord, peripheral nerves or blood vessels may provide the stimulus. Hypersympathotonia has resulted from poliomyelitis, peripheral neuritis,² direct trauma to the cord or peripheral nerves, neuroma,³ inflammatory diseases of the peripheral vessels and frostbite of the extremities. An interesting localized type is that which accompanies local inflammatory lesions about the extremities.

CLASSIFICATION

Since the etiology of hypersympathotonia is not clear in the majority of cases, it is not possible to give an accurate classification. From the analysis of sixty-one of our cases the classification is given in Table I.

The cases may be divided into two large groups: primary and secondary hypersympathotonia.

In the primary form there is no known organic lesion causing the symptom complex and the entire sympathetic system is affected. It usually manifests itself early in life and may be congenital or acquired. Our youngest patient was 8 months old; the oldest was 70 years of age. It is often familial in character. In our series there have been as many as five members of one family affected; three in another and two in several families. Female subjects are affected more often than male.

The group classified as secondary hypersympathotonia includes those patients in whom the disease followed some known exciting cause. Usually only part of the sympathetic system is involved. The exciting cause has been either an injury or an inflammatory process involving some part of the peripheral nervous or vascular systems. The traumatic nerve injuries are usually not severe enough to cause paralysis. In one of our patients a fracture of the cervical

extremities. Often, blotchy cyanosis extended up to the trunk. In none of these patients has there been blanching of the digits as seen in Raynaud's disease. Arterial pulsations of the pedal vessels were often diminished and not demonstrable in some. In several the disability from impaired circulation led



A. BEFORE SYMPATHECTOMY



B AFTER SYMPATHECTOMY

SWEATING REACTION FOLLOWING INJECTION OF PILOCARPINE

Fig 1—Excessive sweating of hand demonstrated by Minor test. Note small nonsweating area. Sweating was abolished temporarily by local Novocain infiltration. In lower frame A shows sweating reaction to pilocarpine when injected intradermally before sympathectomy. B same test after sympathectomy.

edly disturbing. Several of our patients presented a history of mild hyper sympathotonia from childhood, and on being placed in the military service their symptoms became so aggravated that they received medical discharges. In others the symptoms were of little consequence until the patient reached adolescence. In some the stress of earning a living in a competitive business world caused such marked increase in severity of symptoms that they had to give up their work.

The main signs are excessive sweating and vasospasm. These signs are intermittent and remittent. All sympathetic irritants cause aggravation of the symptoms. Chief among these are fatigue, mental anguish, smoking, anxiety, and pain. It has been noted that these patients can be induced, to sweat with tests that do not ordinarily affect normal individuals. We have found that scratching the skin with a sharp needle or performing a venipuncture may induce profuse sweating and marked vasospasm in these patients. Intradermal injections of a weak solution of pilocarpine will cause widespread sweating in the immediate area of the injection (Fig. 1). A weak nicotine solution will also produce such a reaction. The medial aspect of the foot is a good region to apply these tests (Fig. 2). In order to picture the intensity of sweating the Minor's test* is quite useful (Figs. 2 and 3).

It is the excessive sweating that has been most distressing to the majority of these patients. The sweating is usually intermittent. During certain periods of the day the sweating may subside and all seems well. Then suddenly beads of sweat begin to form, coalesce, and drip from the skin. Although sweat glands are distributed over practically the entire surface of the body, the hands, feet, and forehead have the greatest number per square inch.* Under normal conditions these areas most abundantly provided with sweat glands do not sweat most profusely** but in the primary form of hypersympathotonia these areas show the most activity. In the secondary form the excessive sweating is limited to the area stimulated.

The usual stimuli which produce normal excessive sweating also cause excessive sweating in the hypersympathotonic subject. In fact these subjects respond more profusely and more readily to high temperatures and muscular exercise. A striking difference between the normal subject and the person with hypersympathotonia is the reaction to a cold environment. Normally, when the temperature of the environment falls to 70° F. sweating is at a minimum and on lowering the temperature further sweating ceases. The person with hypersympathotonia on the other hand may sweat profusely at a temperature of 70° F. and may continue to sweat at even lower temperatures.

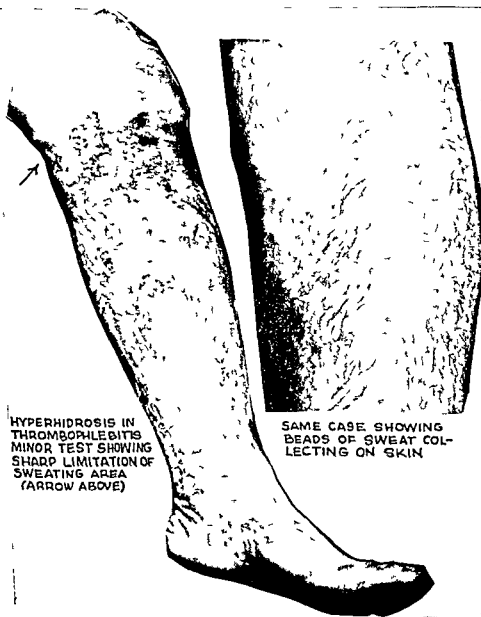
The majority of our patients showed signs of vasospasm. Vasoconstriction is more evident in a cool environment. When examined at a room temperature of 68° F. these patients have exhibited varying degrees of cyanosis of the nail beds of the fingers and toes. This sign was usually more marked in the lower

* Minor's test. Solution is made up of the following constituents: Iodine 1.5— Gm. Eosin 0.1— Gm. Distilled alcohol to 100 cc. This solution is applied to skin that is clean and dry and the area is dusted with fine starch powder. In the presence of sweat the starch iodine reaction will result giving a blue black to violet black color.

had developed chronic lymphangitic edema. Local infections and injuries in variously were slow to heal and often caused exacerbation of sweating and vasoconstriction.

INDICATIONS FOR SURGERY

Sympathetic interruption causes local vasodilatation and checks normal as well as excessive sweating. According to White¹⁰ the first attempt at neuro-



HYPERHIDROSIS IN
THROMBOPHLEBITIS
MINOR TEST SHOWING
SHARP LIMITATION OF
SWEATING AREA
(ARROW ABOVE)

SAME CASE SHOWING
BEADS OF SWEAT COL-
LECTING ON SKIN

FIG. 2.—Excessive sweating in superficial thrombophlebitis. Note that sweating is limited to the inflammatory zone of thrombophlebitis. In upper right portion a section from photo-graph of leg shows great beads of sweat.

them to seek medical advice. In those patients with severe spasm, impaired circulatory manifestations were noted. These included easy fatigue, night cramps in the legs, intermittent claudication and occasionally venous thrombosis. In several of the patients a diagnosis of thromboangitis obliterans had been made. Biopsies of the vessels and response to treatment proved such a diagnosis incorrect. Local skin infections were common and several patients



Fig —Local sweating reaction to pilocarpine intradermally. Arrow point shows site of injection. Minor starch test shows widespread sweating.

environmental temperatures mild sweating can be demonstrated in the sympathetomized areas. Pilocarpine will also produce sweating but to a very mild degree (Fig 1). Nicotine fails to excite sweat gland activity. However, smoking may cause vasoconstriction. In three patients in whom a bilateral cervico-dorsal sympathectomy was performed there has been a recurrence of mild vasospasm in one of the upper extremities. This has been added proof of the presence of vasoconstriction in hypersympathetonia and probably resulted from an incomplete sympathectomy. In all of the remaining patients the vasospastic symptoms have been alleviated. The fatigue, night cramps and intermittent claudication have been relieved.

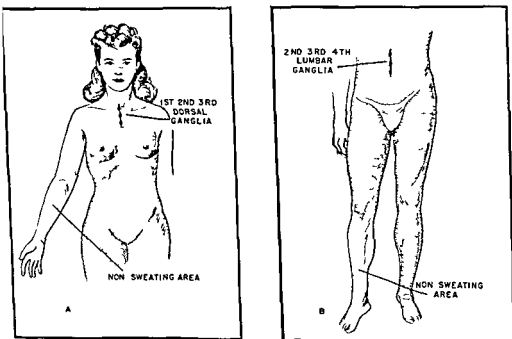


Fig 4—Showing dry areas following cervico-dorsal and lumbar sympathectomy. The sweating area is diminished and may function excessively under proper stimulation. A Area controlled by first, second and third dorsal ganglia. B Area controlled by second, third and fourth lumbar ganglia.

Special comment should be made about those patients in whom a quadrilateral sympathectomy was done. These operations of course deprive the patient of a large number of actively functioning sweat glands. The operations checked sweating of the arms, upper chest, neck, and head. If we add to these areas those eliminated by bilateral lumbar sympathectomy, the feet and legs, the dry portion of the body surface is quite extensive (Fig 4). That portion of the body in which the nerve supply to the sweat glands remains intact responds to certain forms of sympathetic stimulation by sweating excessively. This has been quite a problem for a few of our patients in the hot and humid summers of Washington. Those employed in occupations that require consider-

surgical treatment for hyperhidrosis was performed by Kotzareff in 1919. The operation was partial resection of the cervical ganglia for unilateral hyperhidrosis of the face. In 1935 Adson, Craig and Brown¹ reported the success of sympathectomy in the treatment of hyperhidrosis. List and Plet² have added to our knowledge of the regional sympathetic nerve distribution to the sweat glands. There are many reports demonstrating the success of sympathectomy in the treatment of this condition. However, many patients suffering from this disease are denied the benefit of sympathectomy. This may be because the physician has not been informed of its success or may feel that sympathectomy is yet a too radical procedure.

There are many mild cases of hypersympathetonia that do not require any form of treatment. Some of these persons may have bouts of exacerbations during periods of intense stress and strain which usually subside when equilibrium is restored. Certain persons however, have such marked symptoms which are so persistent that they become a real handicap. Excessive sweating of the hands may become a social and occupational handicap. Several of our female patients found that they were so embarrassed by their cold sweating hands that they refused all forms of social activities. One young lady carried six pairs of white cotton gloves to her dances and changed them frequently as they became damp. A young artist failed in his first professional job because he spoiled all of his drawings by dripping sweat. Some were unable to wear hose because their legs and feet were always wet. One young lady ruined twenty-three pairs of shoes in one year through excessive sweating of the legs and feet. In some of our cases vasospasm had reached such a degree that symptoms of impaired circulation were quite disturbing. Fatigue of the lower extremities was a common finding. In several there was actual intermittent claudication. There were also several instances of venous thrombosis resulting from persistent vasospasm. These severer forms of hypersympathetonia we believe, should have the benefit of sympathectomy.

RESULTS OF SYMPATHECTOMY

In this series of sixty-one patients there were only twenty-three subjected to surgery for a total of seventy-two operations (Table II).

TABLE II

	CASES	OPERATIONS
Combined bilateral cervicodorsal and lumbar sympathectomy	14	50
Lumbar sympathectomy	7	10
(Bilateral 6, one extremity 1)		
Cervicodorsal	2	3
(Bilateral 1 one extremity 1)		
Total	23	72

We have used the preganglionic cervicodorsal sympathectomy¹¹ for the upper extremities and for the lower extremities the second, third and fourth lumbar ganglia have been resected. The end results have been uniformly good and the symptoms have been relieved. There has been no recurrence of sweating. The sweat glands, however, still retain their ability to function. In extreme high

PORTACAVAL ANASTOMOSIS FOR PORTAL HYPERTENSION

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THE control of gastrointestinal hemorrhage and ascites secondary to portal hypertension has long constituted a problem.

Encouraged by early successes in the establishment of portacaval shunts, this series has gradually been expanded to embrace sixty cases.

In the early cases, the nonsuture Vitalium tube method was employed. Noting the tendency of some of the earlier anastomoses to undergo gradual fibrotic occlusion, a shift was made to the suture method. The latter method has long since been employed exclusively. It has the added advantage of conserving the kidney in the splenorenal type of portacaval shunt.

In sixteen of the sixty cases in which portacaval shunts were established (approximately 25 per cent), the functional and pathologic status of the liver was essentially normal. In this group portal hypertension was secondary to a block in the portal bed outside of the liver.

The portal vein itself is so frequently the seat of the obstruction in this type of case as to make one rely primarily upon anastomosis of the splenic vein end to side with the left renal vein for the establishment of a portacaval shunt. This fact alone makes splenectomy contraindicated in such cases unless the surgeon is prepared at the time to proceed with a splenorenal shunt following removal of the spleen. Approximately one half of the shunt failures (twelve in all for the series) are attributable to attempts to save post splenectomy bleeders. Though to include this group gives a less favorable impression to the overall results, it is believed that exploration should be carried out in the patient who is a post splenectomy bleeder with the possibility of establishing some type of portacaval shunt. The likelihood of success is in the neighborhood of 50 per cent.

Upon exploration of the post splenectomy bleeder one will not infrequently find that there is a portion of the stump of the splenic vein remaining unclotted sufficiently long to effect an end to side anastomosis with the vena cava. The inferior mesenteric vein is sometimes sufficiently large to anastomose (proximal) end to side with the left renal vein. Or more frequently the superior mesenteric vein has been employed. The latter though technically more difficult should be employed preferably in side to side anastomosis with the vena cava.

Portal hypertension secondary to cirrhosis of the liver constitutes, in a number of cases by far the greatest problem. Fortunately, in this great group one has an extra choice in vessels, it being possible to employ the portal vein itself in effecting a portacaval shunt.

A decade of experience with the modern medicodietary regimen in the treatment of portal (Laennec's) cirrhosis of the liver has now fairly well

able muscular activity have also witnessed some discomfort from excessive sweating of the trunk. Usually after a year or two sweating becomes more normal.

SUMMARY

A study of sixty one cases of hyperhidrosis has been presented. The essential abnormality is excessive stimulation of the sympathetic nervous system or an increased sensitivity of this system. Excessive sweating has been the predominant symptom, but other signs of sympathetic irritation have usually been present. For this reason we have suggested the term hypersympathotonia to describe this pathologic entity. The etiologic factors have been discussed and a simple classification has been offered. The reasons for selection of certain cases for sympathetic surgery have been submitted. Finally the results of sympathectomy have been presented.

REFERENCES

- 1 Adson A. W. Craig W. M. and Brown G. E. Essential Hyperhidrosis Cured by Sympathectomy. *J. Neurosurg.* 40: 27-43, 1958.
- 2 Lusk, C. F. and Peet M. M. Sweat Secretion in Man. III. *Arch. Neurol. & Psychiat.* 40: 290-296, 1958.
- 3 Kuno Y. The Physiology of Human Perspiration. London 1934. J. & A. Churchill Ltd.
- 4 Weiner J. S. The Regional Distribution of Sweating. *J. Physiol.* 104: 32-40, 1945.
- 5 Weiner J. S. The Regional Distribution of Sweating. Origin and Its Treatment by Sympathectomy. *Ann. Surg.* 135: 1-11, 1952.
- 6 Autonomic Nervous System. New York 1941.

PORTACAVAL ANASTOMOSIS FOR PORTAL HYPERTENSION

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THE control of gastrointestinal hemorrhage and ascites secondary to portal hypertension has long constituted a problem.

Encouraged by early successes in the establishment of portacaval shunts, this series has gradually been expanded to embrace sixty cases.

In the early cases, the nonsuture Vitalium tube method was employed. Noting the tendency of some of the earlier anastomoses to undergo gradual fibrotic occlusion, a shift was made to the suture method. The latter method has long since been employed exclusively. It has the added advantage of conserving the kidney in the splenorenal type of portacaval shunt.

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The portal vein itself is so frequently the seat of the obstruction in this type of case as to make one rely primarily upon anastomosis of the splenic vein end to side with the left renal vein for the establishment of a portacaval shunt. This fact alone makes splenectomy contraindicated in such cases, unless the surgeon is prepared at the time to proceed with a splenorenal shunt following removal of the spleen. Approximately one half of the shunt failures (twelve in all for the series) are attributable to attempts to save post splenectomy bleeders. Though to include this group gives a less favorable impression to the over-all results, it is believed that exploration should be carried out in the patient who is a post splenectomy bleeder with the possibility of establishing some type of portacaval shunt. The likelihood of success is in the neighborhood of 50 per cent.

Upon exploration of the post splenectomy bleeder one will not infrequently find that there is a portion of the stump of the splenic vein remaining unclotted sufficiently long to effect an end to side anastomosis with the vena cava. The inferior mesenteric vein is sometimes sufficiently large to anastomose (proximal) end to side with the left renal vein. Or, more frequently the superior mesenteric vein has been employed. The latter though technically more difficult should be employed preferably in side to side anastomosis with the vena cava.

Portal hypertension secondary to cirrhosis of the liver constitutes in a number of cases by far the greatest problem. Fortunately in this great group one has an extra choice in vessels, it being possible to employ the portal vein itself in effecting a portacaval shunt.

A decade of experience with the modern medicodietary regimen in the treatment of portal (Laennec's) cirrhosis of the liver has now fairly well

established what can and cannot be accomplished. In respect to the incidence and severity of gastrointestinal hemorrhage, for example I am informed by Dr. Arthur Patek, who has been a pioneer in this field that once a patient with cirrhosis has a hemorrhage he has but a 50 per cent chance of being alive one year hence.

Perhaps the greatest achievement of the modern medical regimen in the treatment of Laennec's cirrhosis has been in the relief of ascites. But, here too, there are treatment failures, and in many of this group, the persistence of the ascites is due to the presence of portal hypertension.

There is a growing unanimity of opinion that the medical treatment of post hepatitis cirrhosis is not so satisfactory as that of cirrhosis of the Laennec type. However this may be we are seeing in ever growing numbers cases of post hepatitis cirrhosis in which portal hypertension plays the decisive role.

The porta caval shunt has proved to be a direct and efficient method of reducing portal hypertension in cases of cirrhosis of the liver. With reasonable care in the selection of cases, preoperative preparation and postoperative handling the procedure can be accomplished without unreasonable risks. As a matter of fact in the ten cases in which the portal vein was anastomosed to the vena cava there has been only one postoperative death.

From the standpoint of affording maximum reduction of portal blood pressure the portal vein because of its larger size, is preferable to the splenic vein in the establishment of porta caval shunts in cases of cirrhosis of the liver. The complete disappearance of esophageal varices has been noted as demonstrated by x-ray examination following the establishment of portal vein to vena cava anastomoses.

We are convinced that the portal vein to vena cava type of porta caval shunt has a much higher chance of sustained patency than the spleno renal type of porta caval shunt. There are several logical reasons for this based upon accurate observations.

In the first place the portal vein has a far huskier wall than the splenic vein. It is not necessary to explain what this means to surgeons who have attempted to anastomose veins. This fact plus the supported position of the portal vein within the hepatoduodenal ligament enables it to withstand prolonged periods of portal hypertension without undergoing degenerative changes. In contrast the thinner walled relatively unsupported splenic vein when subjected to a rise in portal pressure becomes dilated, elongated and tortuous. Degenerative changes in the wall consisting of areas of atrophy to tissue paper thinness and the development of intimal sclerotic plaques appear relatively early.

In performing the spleno renal anastomosis there is more likelihood of twisting the splenic vein or the occurrence of angulation compression than obtains in performing the portal vein to vena cava type of porta caval shunt. In mobilizing the splenic vein unlike the portal vein it is necessary to ligate many branches which penetrate the pancreas. The latter is a vascular organ and hemorrhage must be controlled with suture ligatures. Aside from the

many ligated branches affording a nidus of thrombus within the splenic vein, the mass ligatures in the plicatures introduce another possible hazard. As has been frequently observed, the splenic vein lies for a portion of its length in a sulcus upon the pancreas. This places the thin walled vessel in direct contact with areas of pancreatic tissue which have been strangulated by suture ligatures. Opportunities have presented to observe that there can be fibrous tissue residual in these areas which raises the question of possible late compression of the splenic vein itself.

Though the comparative advantages of the portal vein to vena cava type of portacaval shunt were early appreciated it was used with extreme caution. There are now four patients with portal vein to vena cava anastomoses end to side who have been followed in excess of two years. No essential differences have been noted in the behavior of the cirrhotic livers from comparative cases in which the splenorenal type of portacaval shunt has been employed. Thus being reasonably sure of the ground the use of the portal vein in cases of cirrhosis of the liver has more recently been expanded.

In June 1947, while watching Heeney and Humphreys do a complicated surgical procedure through a right thoracoabdominal approach I was impressed by the good lateral exposure of the hepatoduodenal ligament and the ready access to the vena cava. The good exposure was largely accounted for by partial section of the diaphragm permitting rotation upward of the dependent anterolateral margin of the liver. Needless to say the thoracoabdominal approach through the right diaphragm was promptly employed for the establishment of portal vein to vena cava shunts with satisfaction in proved cases of cirrhosis of the liver.

I have recently presented a technique for side to side anastomosis of the portal vein to the vena cava. The method has been employed in two cases with satisfaction. In one case an esophagram done before discharge of the patient from the hospital revealed complete disappearance of the esophageal varices. The second patient is doing well but has not yet been discharged.

The side to side type of anastomosis would seem to offer two theoretical advantages over the end to side anastomosis of the portal vein to the vena cava namely: (1) it permits portal blood flow through the liver should ever the pressure relations become conducive to flow. (2) a lessened tendency to thrombosis of the portal vein toward and into the liver. The side to side variety of anastomosis would seem to eliminate any possible objection to the routine employment of the portal vein to vena cava type of portacaval shunt for the relief of portal hypertension in proved cases of cirrhosis of the liver.

A review of the entire series of sixty cases in which portacaval shunts have been established offers encouragement from the successes which fortunately are decidedly in the majority. The real milestones of progress in the experience however mark those instances of failure presenting overt evidence of errors in judgment or technique.

The operations were performed by either Dr. Allen Whipple or myself in 50 of the 60 cases with a loss of 8 cases postoperatively. There were 3 post

established what can and cannot be accomplished. In respect to the incidence and severity of gastrointestinal hemorrhage, for example, I am informed by Dr. Arthur Patck, who has been a pioneer in this field, that once a patient with cirrhosis has a hemorrhage he has but a 50 per cent chance of being alive one year hence.

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A TECHNIQUE FOR DIVISION AND SUTURE OF THE PATENT DUCTUS ARTERIOSUS IN THE OLDER AGE GROUP

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GROSS¹ who performed the first successful ligation of a patent ductus arteriosus again led the way by proving that dividing the ductus was a more effective procedure than ligation.²⁻⁵ Surgeons with experience in this field have confirmed his teachings.⁶⁻⁷ Thus patients with patent ductus arteriosus are offered an escape from the inevitable incapacitation and shortening of life which result from this malformation.⁸⁻¹²

These brilliant results have occasionally been complicated by serious hemorrhage at the time of operation.^{2, 4, 6, 10, 13, 14} We felt that this danger could be decreased by handling a patent ductus arteriosus as we would any other arteriovenous fistula—that is by control of the arterial and venous components before approaching the communication. This would entail first control of the circulation through the artery and the vein above and below the fistula, second division of the connection between artery and vein and third separate repair of the defects in the artery and vein.

Johnson, Jeffers and Margolies¹⁵ first suggested that in the management of a torn ductus arteriosus the pericardial sac should be opened and a piece of hernia tape placed loosely around the pulmonary artery in the same manner as for a pulmonary emblectomy. If bleeding should be profuse at any time it could be controlled momentarily by compressing the main pulmonary artery. Neuhof¹⁶ pointed out that the source of hemorrhage was the posterior surface of the ductus and the cause, in addition to the possible or probable friability of the ductus when it was the seat of endarteritis was the difficulty of dissection in this region. It was apparent that the exposure of the ductus would be facilitated by incising the pericardium and retracting the dilated pulmonary artery. He accomplished this technique successfully in three cases. Wangensteen also employed this technique in difficult cases. While ligating a patent ductus arteriosus (Crisford)¹⁷ had the experience of having the ligature cut through with bleeding from both the pulmonary artery and the aorta. To control the bleeding it was necessary to apply clamps across the aorta above and below the origin of the ductus and to apply a clamp to the side of the pulmonary artery. Since then he has successfully used this technique originally forced on him in thirty-five cases. He feels that it is possible thus to expose all the ductus tissue out of the aortic wall. Normal aortic wall edges can then be sutured. This technique is safer than leaving behind tissue which might later cause difficulty by forming an aneurysm.

This work was aided in part by a grant from the Life Insurance Medical Research Fund held at the recent annual meeting of the Society for Vascular Surgery, Chicago, Ill., June 9, 1948.

operative deaths in the 10 remaining cases of the series bringing the total to 11 deaths for the entire series of 60 cases. Death in the 3 cases from mesenteric thrombosis would on the basis of necropsy findings in 2 appear to be due to retrograde thrombosis from cavernomatous changes in the portal vein in one case, and an ascending thrombophlebitis starting in the hemorrhoidal veins in the other case.

In 8 postoperative deaths the cause of death was as follows: cerebral damage, 2 cases; 1 of cerebral thrombosis, 1 of lenticular degeneration (Wilson's disease), cardiac failure 1 case, shock from intraperitoneal hemorrhage 1 case, gastrointestinal hemorrhage 1 case, cholemia 3 cases.

Considering that there were forty three cases of cirrhosis of the liver in the group the most impressive feature of the entire death analysis is the low incidence of death from liver failure.

In 1940 Dr Robert S. Grinnell reviewed the cases of cirrhosis of the liver at the Presbyterian Hospital in which simple omentopexy operations had been performed. There were some forty odd cases in the series and the hospital mortality approached 50 per cent. This contrast attests to the very real progress that has been made in recent years both in preparing the cirrhotic liver for surgery and protecting it from damage during operation.

In viewing follow up results following the portacaval shunt procedure in cases of cirrhosis of the liver one must keep in mind exactly what can logically be expected of the operation. In the present state of knowledge at least the procedure can be expected to alter the natural history of cirrhosis in so far as it modifies the course of intractable wasting ascites and recurring hemorrhage secondary to portal hypertension.

arteriosum was performed in four dogs. On the basis of this experience, a modification of the Potts-Smith clamp was constructed which has been successfully used in a clinical case.

EXCISION OF THE LIGAMENTUM ARTERIOSUM IN THE EXPERIMENTAL ANIMAL

Through a left fourth interspace incision, the chest was opened and the mediastinal pleura incised posterior to the vagus nerve. The vagus and recurrent laryngeal nerves were freed and a rubber band placed around them for retraction. The aorta was mobilized close to the origin of the left subclavian artery both anteriorly and posteriorly and was surrounded with a rubber tube. The aorta below the ligamentum arteriosum was then surrounded by another rubber tube. The space between the aorta and pulmonary artery was opened up by blunt dissection with a curved hemostat. The pericardium was then opened posterior to the phrenic nerve. The ligamentum arteriosum was freed by following the line of cleavage of the recurrent laryngeal nerve. A suture was then

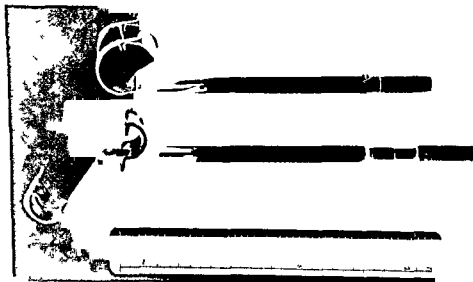


Fig. —Modification of Potts-Smith clamp for occlusion of the origin of a patent ductus arteriosus.

passed about the ligamentum arteriosum and included portions of the wall of the pulmonary artery. At all times good control of the blood flow in the pulmonary end of the ductus arteriosus could be had by digital pressure on the left pulmonary artery through the pericardiotomy incision. With the use of the previously placed rubber tubes for traction the Potts-Smith clamp was placed around the aorta so as to isolate the aortic origin of the ductus when the clamp was closed (Fig. 1). The ligature on the pulmonary end of the ligamentum arteriosum was tied. The ligamentum arteriosum was then divided and the aortic portion of the ligamentum with a small portion of aortic wall excised. The aorta was rotated outward and the opening in the aorta closed with a

It has been found in two cases of surgery of the abdominal aorta, one for arteriovenous fistula¹⁷ and one for aneurysm of the aorta,¹⁸ that prolonged occlusion of the aorta above the renal arteries may lead to a temporary postoperative suppression of renal function associated with transient hypertension. Though Crafoord⁴ reported no evidence of renal damage with his technique of clamping the aorta he did report one case in which the aorta was clamped for twenty five minutes which showed a rather large quantity of urobilin in the

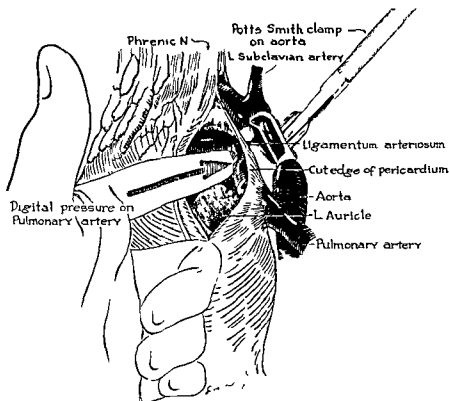


Fig. 1—Technique for excision of ligamentum arteriosum in the L.A. with the use of the Potts Smith clamp.

urine postoperatively. He interpreted this as a sign of impaired liver function due to the lengthy arterial ischemia. Because of these complications it was felt wisest to avoid the use of the aortic clamps. The clamp described by Potts, Smith and Gibson¹⁹ for direct aorta-pulmonary artery anastomosis seemed ideally suited to our purpose for it completely occludes the circulation through the ductus from its aortic end and does not impede free aortic flow.

A plan for the control of the components of the shunt was set up which consisted of (a) pericardiectomy with digital pressure on the left pulmonary artery and (b) a Potts Smith clamp on the aorta. Excision of the ligamentum

arteriosum was performed in four dogs. On the basis of this experience a modification of the Potts-Smith clamp was constructed which has been successfully used in a clinical case.

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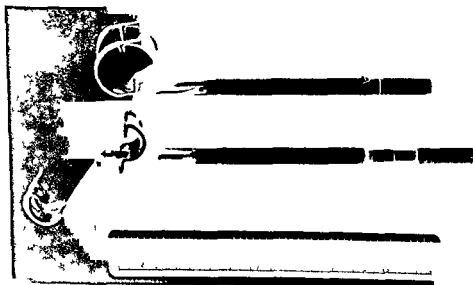


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longitudinal running stitch. The clamp was then released. The pericardiectomy incision was partially closed with two interrupted cotton sutures. The chest was then closed in layers.

Certain difficulties were noted in the use of the Potts-Smith clamp. Because of the straight handle it was sometimes difficult to place the clamp without excessive traction on the aorta. Even though we had access to clamps of several different sizes, there was usually a discrepancy between the diameter of the clamp and that of the aorta. Best results were obtained with a clamp slightly

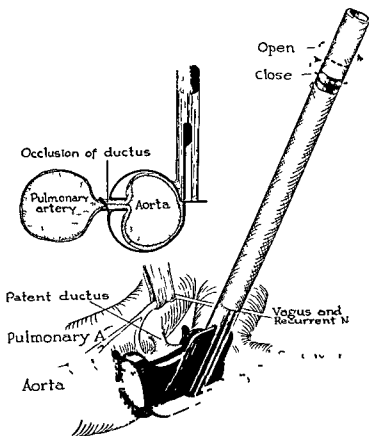


Fig 3—Special aorta clamp in place

smaller than the vessel but then there was a tendency for the aortic wall to bulge forward excessively and also for the back of the clamp to pinch the aortic wall. These difficulties were overcome by designing a clamp* which differed from the usual Potts-Smith in having (a) a swivel handle (b) guides on the lower jaw to prevent bulging of the aorta and (c) a smooth back which could not traumatize the aorta (see Fig 2).

*We are grateful to Mr Elot D. Green of San Francisco for designing and constructing this clamp.

CLINICAL CASE

The patient was a 40-year-old woman with patent ductus arteriosus. Under curare, nitrous oxide, and oxygen anesthesia the chest was entered through a posterior incision. The aorta was found to be greatly dilated at the origin of the ductus, being at least half again as large as it was just above or just below this point. The ductus came off approximately 2 cm. below the origin of the left subclavian artery and was approximately the same size as the subclavian artery. The pulmonary artery was dilated and a pronounced thrill could be felt, especially toward the medial side. The pericardium was incised for a distance of 6 cm. The aorta was encircled by a segment of rubber tubing below the ductus and another just above the origin of the left subclavian artery. By means of traction on these two rubber tubes the aorta was raised from its bed and its posterior surface carefully freed. By means of sharp dissection the space just above the ductus was carefully opened so that it was possible to apply the special aorta clamp (see Fig. 3). The clamp was then screwed down to the point where it obliterated the thrill and was left in place for five minutes while venous pressure readings were taken. The pulse slowed from 80 down to 60, but the venous pressure did not rise. A braided silk ligature was passed above the ductus, being kept anterior to the recurrent laryngeal nerve, but no effort was made to dissect the loose tissue from about the pulmonary end of the ductus. After the clamp was screwed down the ligature was tied as close as possible to the pulmonary artery. The ductus arteriosus was then divided with a knife close to the aorta. The pulmonary end of the ductus distal to the ligature was closed with a continuous over and over stitch. The aorta was then rotated outward and the opening in the aorta closed with a longitudinal continuous over and over stitch of 00000 Deknatel suture. A second running suture was then inserted. On removal of the clamp only minimal bleeding occurred and there was only a slight indentation of the aorta in this region. The opening in the pericardium was closed with interrupted stitches of No. 40 cotton, the parietal pleura over the aorta being sutured in a similar manner. The chest was closed by layers. The patient recovered completely.

DISCUSSION

At the turn of the century Matas²³ stressed the importance of prophylactic hemostasis in approaching an arteriovenous fistula. This prophylactic hemostasis is particularly important in the older age group of patients with patent ductus arteriosus in whom the ductus is friable and in those in whom there is an inflammatory endarteritis. The modified Potts-Smith clamp permits complete control of the aortic end of the ductus arteriosus without interfering with free aortic blood flow. Through the pericardiotomy incision the left pulmonary artery and the pulmonary end of the ductus are controlled. This pericardiotomy incision also facilitates exposure of the ductus.^{16, 17}

In a patient with infection in whom Crafoord¹⁴ had divided and sutured the ductus, a fistula formed between the aorta and pulmonary artery, and he suggested that excision of the diseased walls of the aorta and pulmonary artery would prevent this mishap. With the technique here described it is possible to excise the patent ductus with a portion of the wall of the aorta and pulmonary artery.

Shapiro,¹ Crafoord,¹⁴ and Waugensteen¹⁵ have all reported cases of direct arteriovenous fistula between the aorta and pulmonary artery. The present technique lends itself admirably to the surgical repair of this type of defect.

SUMMARY

A method of prophylactic hemostasis in the surgery of patent ductus arteriosus by the use of a modified Potts-Smith clamp is described.

PREVENTION OF VENOUS THROMBOSIS AND PULMONARY EMBOLISM BY ELECTRICAL STIMULATION OF LEG MUSCLES

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WILLIAM HARVEY, in 1628,¹ first noted that muscular action was important in returning blood from the extremities to the heart. In his words, 'Blood easily concentrates toward the interior as drops of water spilled on a table tend to run together from such slight causes as cold fear or horror. It also tends to move from the tiny veins to the intermediate branches and then to the larger veins because of the movements of the extremities and the compression of the muscles. The importance of muscular action during and immediately after operation prompted this work.

Preventative measures have markedly increased the scope and safety of surgical procedures in recent years. Most prophylactic measures have to do with preparing patients for operation or avoiding complications of the immediate postoperative state and the prevention of pulmonary embolism is within the latter category. The possibility of long continued disabilities and of remote effects which are sometimes more crippling than the disease or condition present before operation should perhaps receive more attention. The prevention of thrombosis not necessarily accompanied by embolism is a problem of magnitude.

Renewed interest in pulmonary embolism and unsatisfactory results in the treatment of varicose veins and other congestive diseases of the lower extremities are two factors in pointing up the necessity for further investigation. The subject of the late sequelae of thrombosis of the leg veins has been repeatedly discussed by John Homans² who also commented on the changes in such problems with recent methods of therapy. These late results often present much difficulty in treatment, permanent edema and functional difficulties of a minor degree being very common. Individuals with ulceration, pain and swelling of the lower extremities can often be helped by proper treatment, but completely satisfactory solution of the problem can come only by prevention of the original thrombosis.

A few years ago heroic operations were occasionally carried out to remove emboli from the pulmonary vessels. Recently, production of a better nutritional state, adjustment of water, salt and protein balance and the free use of blood and plasma have all assisted in reduction of postoperative venous thrombosis. This has been probably due to the maintenance of better circulation during operation and after, and the earlier return to normal reactions accompanied by muscle movements. Early ambulation is possible in more cases today because

¹Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

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REFERENCES

- | | | |
|----|--|--|
| 1 | Gro s, R F, and Hubbard, J I | Surgical Ligation of a Patent Ductus Arteriosus |
| 2 | | Annals of Thoracic Surg 11 314 1947 |
| 3 | | Thoracic Surg 11 314 1947 |
| 4 | Crafoord, C, Mannheimer, F, and Wiklund, T | The Diagnosis and Treatment of Patent Ductus Arteriosus |
| 5 | Brace | Surgical Treatment of the Patent Ductus Arteriosus |
| 6 | Jones | Ductus Arteriosus |
| 7 | Wang | Annals of Thoracic Surg 11 314 1947 |
| 8 | Bullo | Annals of Thoracic Surg 11 314 1947 |
| 9 | Key | Annals of Thoracic Surg 11 314 1947 |
| 10 | Shapiro M J and Key Ancel | The Prognosis of Untreated Patent Ductus Arteriosus and the Results of Surgical Intervention |
| 11 | Tourof Arthur S W | The Results of Surgical Treatment of Patency of the Ductus Arteriosus Complicated by Subacute Bacterial Endocarditis |
| 12 | Gro R F | Surgical Treatment for Cardiovascular Malformations, Tr & Stud |
| 13 | Barn | Treatment of Patent Ductus Arteriosus |
| 14 | Crafoord | Annals of Thoracic Surg 11 314 1947 |
| 15 | Alexander | The Technique of Surgical Treatment of Patent Ductus Arteriosus |
| 16 | | With Special Reference to the Freely Mobile Suture of the Abdominal Aorta |
| 17 | | Annals of Thoracic Surg 11 314 1947 |
| 18 | | Annals of Thoracic Surg 11 314 1947 |
| 19 | | Annals of Thoracic Surg 11 314 1947 |
| 20 | | Annals of Thoracic Surg 11 314 1947 |
| 21 | Mon | Annals of Thoracic Surg 11 314 1947 |

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WILLIAM HARVEY in 1628¹ first noted that muscular action was important in returning blood from the extremities to the heart. In his words: 'Blood easily concentrates toward the interior as drops of water spilled on a table tend to run together from such slight causes as cold, fear or horror. It also tends to move from the tiny veins to the intermediate branches and then to the larger veins because of the movements of the extremities and the compression of the muscles.' The importance of muscular action during and immediately after operation prompted this work.

Preventative measures have markedly increased the scope and safety of surgical procedures in recent years. Most prophylactic measures have to do with preparing patients for operation or avoiding complications of the immediate postoperative state and the prevention of pulmonary embolism is within the latter category. The possibility of long continued disabilities and of remote effects, which are sometimes more crippling than the disease or condition present before operation, should perhaps receive more attention. The prevention of thrombosis not necessarily accompanied by embolism is a problem of magnitude.

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REFERENCES

- 1 Gros R F, and Hubbard, J I Surgical Ligation of a Patent Ductus Arteriosus
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3 A Report
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PREVENTION OF VENOUS THROMBOSIS AND PULMONARY EMBOLISM BY ELECTRICAL STIMULATION OF LEG MUSCLES

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WILLIAM HARVEY, in 1628¹ first noted that muscular action was important in returning blood from the extremities to the heart. In his words, "Blood easily concentrates toward the interior as drops of water spilled on a table tend to run together from such slight causes as cold air or horror. It also tends to move from the tiny veins to the intermediate branches and then to the larger veins because of the movements of the extremities and the compression of the muscles." The importance of muscular action during and immediately after operation prompted this work.

Preventative measures have markedly increased the scope and safety of surgical procedures in recent years. Most prophylactic measures have to do with preparing patients for operation or avoiding complications of the immediate postoperative state and the prevention of pulmonary embolism is within the latter category. The possibility of long continued disabilities and of remote effects which are sometimes more crippling than the disease or condition present before operation should perhaps receive more attention. The prevention of thrombosis not necessarily accompanied by embolism is a problem of magnitude.

Renewed interest in pulmonary embolism and unsatisfactory results in the treatment of varicose veins and other congestive diseases of the lower extremities are two factors in pointing up the necessity for further investigation. The subject of the late sequelae of thrombosis of the leg veins has been repeatedly discussed by John Homans² who also commented on the changes in such problems with recent methods of therapy. These late results often present much difficulty in treatment, permanent edema and functional difficulties of a minor degree being very common. Individuals with ulceration, pain and swelling of the lower extremities can often be helped by proper treatment, but completely satisfactory solution of the problem can come only by prevention of the original thrombosis.

A few years ago heroic operations were occasionally carried out to remove emboli from the pulmonary vessels. Recently, production of a better nutritional state, adjustment of water, salt and protein balance and the free use of blood and plasma have all assisted in reduction of postoperative venous thrombosis. This has been probably due to the maintenance of better circulation during operation and after and the earlier return to normal reactions accompanied by muscle movements. Early ambulation is possible in more cases today because

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of such measures, and its use perhaps reduces the incidence of thrombosis and the spread of incipient thrombi. However, early ambulation does not mean immediate walking and sometimes it cannot be implemented within days or even weeks.

The sources of pulmonary emboli are generally conceded to be in the lower extremities in over 90 per cent of all cases if one excludes from consideration those of purely cardiac origin. The writings of Hunter and his associates³ cover the subject excellently in this respect and again emphasize earlier findings that venous thrombosis in the feet and legs is much more common than generally known.

Various prophylactic measures have been used recently with benefit. Ochsner and DeBakey,⁴ among other measures carry out wrapping of the lower extremities with elastic bandages. These must be applied with care to avoid harmful constrictions and are probably especially useful when patients have sizable varicosities. The Trendelenburg position is useful in preventing pooling of blood but may not be advisable in some types of cases. Elevation of the lower extremities alone may lead to pelvic pooling and we know that sometimes thrombosis begins in the prostatic and other pelvic veins. Allen and his associates⁵ consider adequate measures of such importance that they advocate ligation of femoral veins as a prophylactic measure in selected cases. This does avoid long and deadly thrombi from the thighs and legs and may, by forced utilization of pelvic anastomotic channels cause speeding up of flow through pelvic veins with resulting benefit. However we have felt that a defective venous circulation is thus produced with the possibility of deleterious late effects. The prophylactic use of anticoagulants⁶⁻¹¹ undoubtedly reduces thrombosis but introduces the hazards of hemorrhage if used in adequate dosage. If anticoagulant use is delayed some degree of thrombosis may occur. If formation of incipient thrombi were to be avoided anticoagulants would be necessary during operation which is obviously impractical as a general rule. Early active motion is desirable and universally accepted but methods requiring active co-operation on the part of the patient cannot be instituted early enough for complete protection especially in the presence of serious illness or after extensive operations. In the treatment of patients in whom thrombosis has already taken place we have used the anticoagulant method with satisfaction thus far.

During operation and for some time after the patient's leg muscles are paralyzed by general or spinal anesthesia and the blood pressure is often lowered. In extreme cases the circulation may be markedly slowed. After operation the very sick patient moves his muscles little for a day or even several days and during this time the legs and feet are sometimes immobilized with firm bed coverings. This is also too frequently true of the very ill medical patient with cardiac or other diseases.¹² During this time the patient's legs press upon a firm operating table or mattress and can often be seen to assume a triangular cross section especially in undernourished individuals with soft muscles. Under these conditions not only are the veins compressed but trauma occurs setting up ideal conditions for thrombosis. One need only to observe a

patient operated upon under local anesthesia, using light sedation, to realize that the legs soon become very uncomfortable. Heavy sedation postoperatively, desperate illness or pain elsewhere are the only things that prevent patients from moving about considerably and changing position to avoid such trauma and the accompanying pain. The trauma may be direct to all the tissues, including the veins and aggravated by interference with circulation in capillaries, venules, and veins. It is pertinent that only rarely are the anterior leg veins the seat of the original thrombosis. Likewise forearm and arm veins are seldom the seat of thrombi leading to embolism, except in cases of obstructive lesions. That trauma alone does not lead to massive clot formation is indicated by the relative freedom from this complication in arm veins used for intravenous medication. Here despite puncture and at times irritating solutions even leading to inflammation massive thrombosis is relatively infrequent. Thus it seems that a combination of trauma and stasis is necessary for the formation of thrombi and their growth. A clot which is present only in the leg veins may remain trapped there by the numerous branches and connections between the veins but when it extends into the popliteal and femoral veins, it can be broken loose easily by bending of the knee and the squeezing action of the muscles. The more comprehensive discussions and studies of etiology by Karsner,¹³ Hunter and his associates,³ Frykholm,¹⁴ Smith and Allen,¹⁵ O'Neill¹⁶ and others generally support the need for early prophylaxis.

In view of these facts it was felt that the methods in use while remarkably lowering mortality and perhaps morbidity were still inadequate chiefly because preventative measures were not instituted soon enough. It seemed that a stimulation of the blood flow immediately after operation and even during prolonged operations would reduce the incidence of leg vessel thrombosis. A method not requiring cooperation of the patient was needed and it seemed that electrical stimulation could produce the desired result. It could be applied with no inconvenience to the patient could be used intermittently and even during anesthesia or sleep. Accordingly I saw Dr H. T. Zankel of the Department of Physical Medicine Rehabilitation who suggested that a sinusoidal type of current would give a good reaction without undue disturbance of the patient. A stimulus given to the calf muscles thirty times a minute for one half hour with one half hour rest period and continued for at least twenty four hours was decided upon and we have had no reason to change this during the course of the experiment since early in January 1947. In a few instances treatment has been prolonged for two days. Some patients had a short massage of the leg muscles while still on the operating table and this should be done to all. No attempt was made to determine unusual clotting tendencies before or after operation though this factor is of importance as shown by the work of de Takats.¹ Some patients would probably have profited by a continuation of modified treatment with muscle stimulation carried out four or five times a day. Stimulation sufficient to contract the calf muscles so as to move the foot slightly was the objective and though muscle stimulation was not attempted during this study.

RESULTS

In order to obtain directly comparable statistics this method should be carried on to include about 20 000 patients one half treated and one half untreated, but this would obviously prolong the experiment too greatly before rendering a report, if good major cases were chosen. The results after treating over 800 are encouraging despite the fact that the machines were never used more than two days postoperatively, and no other unusual nursing or medical care was given.

There was no complaint on the part of the patients except for occasional slight burning sensations which could usually be eliminated by readjustment of the electrodes and current. On two known occasions however, the current was apparently too intense and caused subsequent tenderness. This is of special importance in patients with insufficient arterial circulation such as those with arteriosclerosis obliterans. Here especially when narcotics are used close supervision of the technicians is necessary. No other deleterious side effects were noted. The contractions of the calf muscles generally caused slight foot movements, but these did not interfere with sleep. Some patients volunteered the information that it gave them the sensation of having taken a walk, and we feel that the mild exercise provided is beneficial.

During the first three months the apparatus was used mostly on patients who had hemorrhaphy, excision of pilonidal sinus, anal fistulectomy, and even hemorrhoidectomy. For the last fifteen months most of the extensive cases on the general surgical service have been treated choice being based on the extent and seriousness of the operation whenever possible. A large proportion of the patients was in the older age group. Patients with venous ligation of any type were not included in the statistical table for obvious reasons. Those with hemorrhoidectomies and similar procedures treated in the last six months were not included because it was felt that such minor procedures are less likely to produce leg thrombosis and therefore would weigh the results too favorably.

The six cases of venous thrombosis occurring despite this treatment are worthy of some discussion.

CASE REPORTS

CASE 1—This 60 year old man had hemiplegia five years previously with marked residuals. He was admitted with marked anemia, weakness and loss of appetite and was found to have a carcinoma of the cecum and a cecocolic colon. Following multiple transfusions he had a right colectomy with transverse ileocolostomy. The leg muscles were stimulated for two days. One week later he was allowed up and evaserated requiring secondary closure and was again treated by leg stimulation for one day. Three days later he had bilateral bronchopneumonia. Eighteen days after the original operation and eleven days after secondary closure he developed a superficial (saphenous vein) acute thrombophlebitis which gradually involved the great saphenous system to the groin with possible deep extension of some degree. It subsided without incident on anticoagulant therapy which was maintained seven days. Five days after discontinuing Dicumarol he showed evidence of intra abdominal hemorrhage. Hemoglobin was 28 per cent, red blood cells 1.4 million and prothrombin time was 1.0 per cent of normal. Treatment was with vitamin K and 5,500 cc of blood. At the time of discharge there was slight residual swelling of the leg.

CASE 2—This 52 year-old man had had urinary bladder symptoms since 1943. There was a diagnosis, by biopsy of transitional carcinoma in 1945. In January 1946, he had x-ray

therapy and in February, 1947, he was given a second course together with radium treatment. He finally became severely contipated and was admitted in July, 1947. Examination showed induration of the abdominal wall and groins, and skin changes due to irradiation were present. A large mass was palpable through the rectum chiefly on the left side. On August 5, a transverse colostomy was done because of partial obstruction and leg muscles were stimulated for twenty-four hours. There was phlebitis with thrombosis of the arm veins during the immediate postoperative course, but none in the leg. On August 15 twenty days after colostomy thrombophlebitis was first found affecting the saphenous veins. Later the calf veins were involved. Recovery from the thrombophlebitis was uneventful but the patient subsequently died with bronchopneumonia.

CASE 3—Exploration was done on an elderly man and he was found to have an inoperable carcinoma of the stomach. Peritoneal implants were found in the pelvis though without any large mass. He was treated with leg stimulation for only one day and it was not started until three hours after operation. There was postoperative gastric dilatation and thus on the fourth day after operation there was a rapidly developing thrombophlebitis of the entire left lower extremity with little discomfort. During the next two days, edema involved the scrotum and inguinal regions but later subsided. He had no specific treatment for the thrombosis except elevation, but the swelling subsided to a considerable extent.

In none of these three cases did the thrombosis originate within the calf veins, the usual site of origin of the silent type of thrombosis or phlebothrombosis. In the first it is interesting that despite all the patient's troubles thrombosis did not occur until well along the course after a bout of pneumonia. Perhaps he needed circulatory stimulation during the pneumonia more than at other times. The second was really a case of terminal care. The fact that thrombosis in the legs was avoided for so long was remarkable in view of the thrombosis in the arms and the pelvic tumor mass. It is felt that the treatment delayed leg vein thrombosis, which occurred almost three weeks after the exploration. The course indicates that he was the type with a tendency to thrombosis. Only in Case 3 did the complication occur soon after operation, and here it probably was primarily pelvic vein thrombosis. This man's blood pressure was subnormal during the first two days and treatment should have been started sooner and prolonged for at least another day. The diagnosis no doubt tended to preclude vigorous therapy.

CASE 4—This man was 62 years old with diabetes and arteriosclerotic gangrene of the left foot necessitating a mid thigh amputation on Oct 8, 1944. After a good recovery right lumbar sympathectomy was done on November 3. One day after operation, he complained of some soreness of the right calf and the following day a superficial vein was found thrombosed. This was treated with anticoagulants and he did not develop any swelling or extension of the process. The leg appears normal at present.

CASE 5—A man of 50 years with perforated gastric ulcer had the perforation sutured under general anesthesia. Four days after operation despite a one-day treatment by leg stimulation he developed a typical thrombophlebitis of the right calf with extension upward to the thigh. He responded well to anticoagulant therapy.

CASE 6—This 60 year old man had a large right direct inguinal hernia. There was some peripheral edema. The heart was normal in size, there was a systolic murmur and the blood pressure was 140/100. There was a small emphysema. Right inguinal herniorrhaphy required considerable time, the Halter presenting in the sac. In the repair Cooper's ligament was utilized. Temperature on the fourth day reached 101. In the calf tenderness was present on the right. He was treated with anticoagulant but also developed left calf ten-

dermess with a positive Homans sign the following day. However temperature returned to normal on the sixth day and remained so thereafter. No demonstrable swelling occurred. The patient had received forty-eight hour treatment but it was not started for some time after return from the operating room.

These last three patients had involvement of calf veins, though the phlebitis in Case 4 was quite superficial. In this patient the treatment was probably too vigorous. This was a dangerous type of case with recent thrombosis of arteries of the other leg and an impaired arterial circulation in the leg under treatment.

A study of Table I indicates that with the exception of the first two classes we have chosen to treat cases of truly major caliber. Among those patients with acute appendicitis were some who traveled considerable distances to reach the hospital. A large proportion of the patients was in the older age groups as indicated by the types of operations necessary even in the hernia group 46.4 per cent of them were over 40 years of age. Many of the patients had been hospitalized elsewhere previously. To counterbalance this the preoperative and postoperative care was of the highest order and intravenous therapy was used fully as required. Operations were performed by a number of surgeons, a considerable portion being done by the resident staff.

TABLE I

TYPE OF CASES	TOTAL	WITH THROMBOSIS
Anorectal including hemorrhoidectomy	16	
Pilonidal sinus, fistula perirectal abscess	66	
Hernia including bilateral femoral and many with Cooper ligament type of repair	259	1
Ventral hernia	13	
Miscellaneous extensive procedures including jaw resection		
grafts tumors	70	
Appendectomies chiefly emergency	71	
Cholecystectomies duct explorations	4	
Major gastric including resection gastroenterostomy plus vagotomy	4	1
Miscellaneous abdominal including resection of tumor, exploration with colotomy abscess	42	2
Intestinal resections	1	1
Major thoracic, chiefly lobectomies	4	
Vagotomies	3	
Sympathectomy dorsal or lumbar	3	1
High amputations	10	
Total	69	6
With thrombosis	6 per cent	
Embolism	0	

Our files are not extensive enough to furnish figures for comparison but based on general experience with operations of like nature we might conservatively have expected an incidence of thrombosis of 4 or 5 per cent. Despite the fact that most of our serious cases were treated by stimulation there were some patients who because of lack of apparatus or other considerations were not included. Among these were four patients who had pulmonary embolism one of them dying. This is pertinent in that there was not one case of embolism in our treated series. While it should be noted here that four of our six cases

of thrombosis were treated with anticoagulants after the diagnosis was made, the evidence indicates that prevention of incipient thrombosis has led to decrease in the extensive type of thrombi that cause embolism. This is a desirable important corollary to our chief aim, which is the reduction of morbidity from thrombosis of lower extremity veins in general.

DISCUSSION

Modifications of this treatment will undoubtedly be made in the future and there is no reason why treatment should have been limited to the immediate postoperative period other than definite control for purposes of accurate study. Treatments were given under the supervision of the physiotherapy department by ward attendants. It is best when ward surgeons designate specifically the amount of treatment and also make occasional observations on the efficacy of the stimulation. One factor of importance is the beginning of the treatment as soon as the patient is returned to the ward.

There are no absolute contraindications to use of this therapy but in patients with impaired arterial circulation caution must be exercised. Possible difficulties in conditions such as arteriosclerosis obliterans or Buerger's disease include injury to muscles by local overheating or forced exercise beyond the fatigue point.

While our series is not large * results thus far indicate that one can expect a marked drop in the incidence of leg vein thrombosis by electrically stimulating the leg muscles during the time that circulation is impaired, in patients undergoing operation. Most important is the fact that this is accomplished with few deleterious side effects and with a minimum of expert care. The effectiveness of such treatment given only a few times a day is still to be determined. It has the further advantages of mildly exercising the muscles regularly without interfering in any way with other treatment and may thus be useful in general medical diseases and in the treatment of victims of fractures.

A project such as this requires the cooperation of many workers and the writer gratefully acknowledges that given by the entire Surgical Staff and the staff of the Department of Physical Medicine Rehabilitation of Grille Veterans Hospital.

REFERENCES

- 1 Harvey William. Anatomical Studies on the Motion of the Heart and Blood. The Leake Translation Springfield Ill 1931 Charles C Thomas Publisher
- 2 Homans John. Circulatory Diseases of the Extremity. New York 1939 The Macmillan Company.
- Idem. The Late Results of Femoral Thrombophlebitis and Their Treatment. New England J Med 235 1931 1941
- 3 Hunter W C Sneed A D Robertson T D and Snyder C A C. Thrombosis of the Leg Veins. J Surg 1931 39: 1-10
- 4 Ochs Ochs
- 5 Allen

* Since submission of this report 409 additional patients have been treated with continued good results.

A COMPARISON OF SYMPATHOLYTIC EFFECTS OF PRISCOL,* ETAMON,† AND DIBLAMINE‡ IN DOGS WITH RESULTS OF ACTUAL SYMPATHETOMY

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POSSIBLE clinical use for sympatholytic drugs has been established by surgery. Removal of upper dorsal or lumbar portions of the sympathetic nervous system aids treatment of certain patients with peripheral vascular disease.¹ Sympathetic denervation of the splanchnic area, lower trunk, and occasionally legs (Smithwick)² or denervation of most or all of the body, including thoracic as well as splanchnic visceral areas and head, arms, and upper trunk together with part or all of the lower trunk and legs,³ has aided treatment of many patients with hypertension.

Potential use for sympatholytic drugs as aids to diagnosis or prognosis also has been established by surgical methods. Temporary block of lumbar or upper dorsal sympathetic ganglia by injection of a local anesthetic and block of preganglionic fibers to the legs with spinal anesthetic have been recommended as methods of determining indications for sympathectomy in patients with peripheral vascular disease. Also, high spinal anesthesia has been suggested as a method of determining advisability of sympathectomy for hypertension.

Either local block or spinal anesthesia may produce changes of circulation simulating immediate results of sympathectomy but may fail to predict lasting results of chronic denervation which would be effected by operation. Immediate changes in circulation might be estimated by drugs capable of duplicating effects of sympathectomy. Also effects of chronic denervation and results of actual sympathectomy might be predicted by use of such drugs if therapeutic effects could be maintained during treatment lasting several days or longer. Finally, a safe sympatholytic drug, effective during continuous treatment, might replace sympathectomy in certain patients or aid in the treatment of others in whom operation is contraindicated.

Most of the newly developed sympathetic blocking drugs are first adrenolytic; small doses blocking the blood pressure elevating action of epinephrine. In one field of surgery, particularly, this would be important. Diagnosis of pheochromocytoma or paraganglioma is often uncertain. When diagnosis is confirmed by exploration, removal of the tumor is associated with risk of shock from epinephrine intoxication. Preoperative preparation by an adrenolytic drug might aid diagnosis and possibly treatment of these tumors.

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Adrenolytic and sympatholytic drugs have been known for many years and many new preparations have been and are being developed. Among the earlier drugs ergotoxine, the Fourneau compound F 933,* and yohimbine are described as primarily and predominantly adrenolytic. Ergotamine tartrate and F 893 are said to be predominantly sympatholytic. Investigation of these compounds gave promising experimental results but usually toxicity or undesirable side effects discouraged use clinically.

Three new drugs have currently received clinical trial and have been judged reasonably safe. These are Priscol (2-Benzyl-4,5-imidazoline hydrochloride), I tamon (tetraethylammonium chloride or bromide) and Dibenamine (dibenzyl-beta-chloroethylamine hydrochloride). Literature describing special properties of these drugs has been reviewed by Ahlquist and associates,⁴ Acheson and Moc⁵ and Nickerson and Goodman⁶ respectively, as well as by many others. Therefore only a brief summary of currently accepted properties will be presented.

In 1939 blood pressure depressing action of Priscol was described by Hartmann and Isler.⁷ Meier and Mueller⁸ noted dilatation of vessels of mucosa and skin. Hatt⁹ using the Starling heart lung preparation found damaging doses of Priscol are 100 times greater than those used to reduce blood pressure. Priscol evidently stimulates cardiac output and produces vasodilatation of coronary vessels. Adrenolytic action was noted by Meier and Mueller⁸ and was clarified by Meyer¹⁰ and Chess and Yonkman.¹¹ Cholinergic action on ileum of dogs was described by Yonkman, Hays, Cameron, Pellett and Hansen.¹² Ahlquist and Woodbury¹³ observed that Priscol inhibits pressor and constrictor effects of sympathomimetic drugs but has little effect on depressor and dilator actions. Ahlquist, Huggins and Woodbury¹⁴ reported that Priscol has complex pharmacologic actions which vary in different species. For example, the drug produces sympathomimetic and adrenolytic as well as acetylcholine like effects.

Blocking action of Priscol apparently occurs at end organs of the adrenergic components of the sympathetic nervous system. Evidently only excitatory pathways are blocked and the inhibitory pathways remaining are relatively unaffected. Priscol is effective when given orally, intramuscularly, or intravenously.

The literature describing clinical use of Priscol for patients with peripheral vascular disease and hypertension has been reviewed in a separate report.¹

Properties and site of action of tetraethylammonium chloride or bromide have been studied extensively by Acheson, Moc and their associates,⁵ Berry, Campbell, Lyons, Moc and Suttler,¹⁵ and many others. Acheson and Moc⁵ demonstrated that the tetraethylammonium ion exerts its effect by blocking efferent pathways in autonomic ganglia. Acheson and Pereira¹⁷ suggested that action within the ganglion is similar to the ganglionic blocking action of curare. The tetraethylammonium ion does not block pressor action of epinephrine. It is effective when given intramuscularly or intravenously but not when given orally.

Properties of Dibenamine have been reported chiefly by Nickerson and Goodman.⁶ They demonstrated that it is an effective adrenolytic and sympatholytic agent. Mode and site of action are thought to be similar to that of

*Since this manuscript was written, Goldsberg, M., Enjler, C. H. and Aranow, H. J. A. M. A. 153: 971-9, 1949 have reported clinical use of F 933 as a diagnostic agent in adrenalinoma.

Priscol, that is block of end receptors of the sympathetic nervous system. It is of interest that effects of this drug may persist twenty four hours or longer. Recent reports of clinical trial have confirmed these properties but have indicated possible toxic effects in the central nervous system even with relatively small dosage.¹⁸ Dibenamine usually has been given intravenously since necrosis results with other parenteral routes and it may not be well tolerated by mouth. Because of desirability of developing sympatholytic and/or adrenolytic agents for possible clinical use, this experimental study of drug effects was undertaken in dogs. A comparison of the effects of each of the three new drugs was desired. Experiments were designed to test reflexes known to be abolished in dogs by total sympathectomy or by lumbar ganglionectomy.

Complete sympathectomy in dogs abolishes the carotid sinus pressor reflex elevation of blood pressure with stimulation of the central end of divided vagus nerves and the pressor response to anoxia.^{1,19} It also lowers mean systolic blood pressure to values around 80 to 100 mm Hg. Complete sympathectomy neither abolishes nor increases pressor responses to epinephrine. Lumbar sympathectomy abolishes active reflex changes of peripheral resistance as judged by the Nolf three way cannula methods.²⁰

Experiments were therefore designed to compare effects of Priscol Etamon and Dibenamine with these effects of sympathectomy. In addition, experiments were designed to test action of epinephrine and other drugs. Preliminary abstracts have been presented.^{21,22,23,24}

METHOD

Healthy dogs weighing 10 to 17 kilograms were used in all experiments. Each was anesthetized using chloralose 0.1 Gm per kilogram administered intravenously. The trachea was isolated through a midline incision in the neck and a cannula inserted. Carotid arteries on each side were identified. Vagus nerves were dissected free and divided. Next a unilateral lumbar sympathectomy was performed through a midline transabdominal approach. The femoral artery of each leg was exposed and divided one inch below the inguinal ligament. Systemic arterial blood pressure was recorded using a mercury manometer attached to a cannula in the proximal end of the divided artery of the non-sympathectomized extremity. Mercury manometers were also attached to cannulas in the distal ends of each of the divided femoral arteries to yield an indirect measurement of peripheral resistance as described by Nolf. Respiratory activity was recorded by means of a pneumograph connected with a tambour. All measurements were recorded continuously using a kymograph. Hemostasis was carefully maintained throughout each experiment.

Since a comparative assay of action of the three drugs was desired a series of tests of vasomotor reflexes and responses to epinephrine was planned and executed during each experiment. Four or more experiments were conducted with each drug using a freshly prepared animal each time and repeating a series of tests several times in each animal. Tests included bilateral occlusion of the common carotid arteries using bulldog arterial clamps and maintaining occlusion one minute, intravenous injection of 0.03 mg of epinephrine, stimulation of

proximal segments of a divided vagus by a faradic current and anoxia or asphyxia. Other tests occasionally employed were stimulation of the distal end of the right vagus nerve and administration of pituitrin or prostigmine. During each test changes of pulse, systemic blood pressure, peripheral femoral blood pressure, and respiration were noted.

This series of tests was performed before and after administration of each of the three drugs. Priscol, I tamon, or Dibenamine were given in varying doses. When a small dose was used initially, progressively larger doses were injected and each was followed by repetition of tests. Large or consistently effective doses were administered by the end of each experiment.

EXPERIMENTAL RESULTS

Priscol

Blood Pressure and Pulse—Priscol in amounts varying from 0.05 to 7 mg per kilogram was given intravenously as an initial dose in six animals. No change of blood pressure was produced by 0.05 mg per kilogram in one animal

a rise from 160 to 230. Blood pressure remained elevated 8 to 16 minutes. The sixth dog given 7 mg per kilogram responded with a temporary elevation followed by a gradual decline (Fig. 1). After intervals of approximately one half hour five of these dogs were again given Priscol intravenously. Subsequent injections varied in number from three to nine; individual doses varied in amounts from 0.37 to 9.0 mg per kilogram, and total dose varied from 6.4 to 35 mg per kilogram. Each subsequent injection produced decrease of blood pressure in three dogs. A one minute rise followed by decline occurred in one after 5 mg per kilogram. The fifth dog which had a rise from 124 to 199 following the initial 0.6 mg per kilogram also had similar rises after 1.2 and 3.6 mg per kilogram. Subsequent injections of 6.0 and 9.0 mg per kilogram, however, produced decreases of pressure. In all six animals a gradual decline of blood pressure started after the initial or the first subsequent injection of Priscol and continued throughout the experiment finally reaching shock levels below 70 mm Hg. Also in each of the six pulse rate consistently increased following the initial dose and throughout subsequent injections remained 20 to 50 beats per minute faster than before Priscol.

Carotid Sinus Reflex—Before Priscol occlusion of both carotid arteries produced elevations of mean systolic blood pressures in six animals. Increases ranged between changes from 125 to 184 mm Hg in one animal to 140 to 220 mm Hg in another. After initial injection of 0.05 mg of Priscol per kilogram in one animal and 0.07 mg per kilogram in two others reflexes and blood pressure were only slightly depressed. After 0.6 mg per kilogram in one dog mean systolic blood pressure increased and the reflex was reversed, lowering being from 178 to 148. Subsequently following larger doses in this animal the reflex increased pressure. After 2.0 mg per kilogram in another the reflex was not changed. Following the single dose of 7 mg per kilogram in one animal reduc

tion of mean blood pressure and finally block of the carotid sinus reflex occurred (Fig 1). Four of the five dogs receiving subsequent injections decreased the reflex response to rises between 130 to 146 and 106 to 126 after 0.5 to 10 mg per kilogram. Response was finally blocked after doses of 6 to 25 mg following

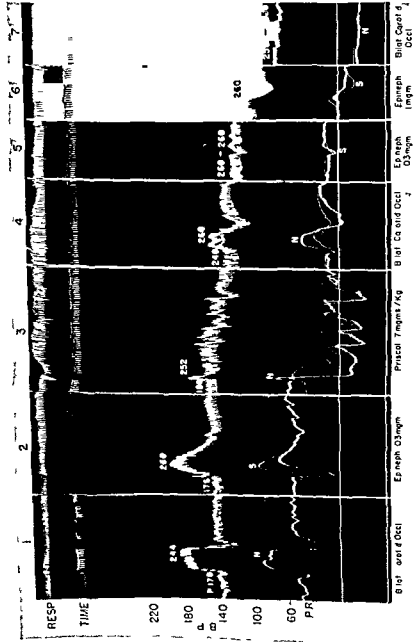


Fig. 1.—Effects of occlusion of both carotid arteries and of intravenous injection of 0.3 mg of epinephrine upon respiration in a systemic hypotensive blood pressure animal upon back pressure of a normally innervated limb (N) and of a sympathetomized limb (S) as shown in panel 1. Administration of 7 mg per kilogram (panel 3) produced increase of pulse rate and peripheral decrease of systolic blood pressure (marked decrease of back pressure of the normal limb occurred that of the sympathetomized limb of lining more gradually). The four panels on the right demonstrate completely by occlusion of carotid sinus reflex block of response to epinephrine and finally complete block of reflex to carotid occlusion. Blood pressure gradually returned during the experiment.

proximal segments of a divided vagus by a faradic current and anoxia or asphyxia. Other tests occasionally employed were stimulation of the distal end of the right vagus nerve and administration of pituitrin or prostigmine. During each test changes of pulse, systemic blood pressure, peripheral femoral blood pressure, and respiration were noted.

This series of tests was performed before and after administration of each of the three drugs. Priscol, Etamon or Dibenzamine were given in varying doses. When a small dose was used initially, progressively larger doses were injected and each was followed by repetition of tests. Large or consistently effective doses were administered by the end of each experiment.

EXPERIMENTAL RESULTS

Priscol

Blood Pressure and Pulse—Priscol in amounts varying from 0.05 to 7 mg per kilogram was given intravenously as an initial dose in six animals. No

a rise from 160 to 230. Blood pressure remained elevated 8 to 16 minutes. The sixth dog given 7 mg per kilogram responded with a temporary elevation followed by a gradual decline (Fig. 1). After intervals of approximately one half hour five of these dogs were again given Priscol intravenously. Subsequent injections varied in number from three to nine; individual doses varied in amounts from 0.37 to 9.0 mg per kilogram and total dose varied from 6.4 to 35 mg per kilogram. Each subsequent injection produced decrease of blood pressure in three dogs. A one minute rise followed by decline occurred in one after 5 mg per kilogram. The fifth dog, which had a rise from 124 to 188 following the initial 0.6 mg per kilogram, also had similar rises after 1.2 and 3.6 mg per kilogram. Subsequent injections of 6.0 and 9.0 mg per kilogram, however, produced decreases of pressure. In all six animals a gradual decline of blood pressure started after the initial or the first subsequent injection of Priscol and continued throughout the experiment finally reaching shock levels below 70 mm Hg. Also, in each of the six pulse rate consistently increased following the initial dose and throughout subsequent injections remained 20 to 50 beats per minute faster than before Priscol.

Carotid Sinus Reflex—Before Priscol, occlusion of both carotid arteries produced elevations of mean systolic blood pressure in six animals. Increases ranged between changes from 128 to 184 mm Hg in one animal to 140 to 220 mm Hg in another. After initial injection of 0.05 mg of Priscol per kilogram in one animal and 0.07 mg per kilogram in two others, reflexes and blood pressure were only slightly depressed. After 0.6 mg per kilogram in one dog mean systolic blood pressure increased and the reflex was reversed, lowering being from 178 to 148. Subsequently following larger doses in this animal the reflex increased pressure. After 2.0 mg per kilogram in another the reflex was not changed. Following the single dose of 7 mg per kilogram in one animal, reduce

tion of mean blood pressure and finally block of the carotid sinus reflex occurred (Fig 1). Four of the five dogs receiving subsequent injections decreased the reflex response to rises between 130 to 146 and 106 to 126 after 0.5 to 10 mg per kilogram. Response was finally blocked after doses of 6 to 25 mg following

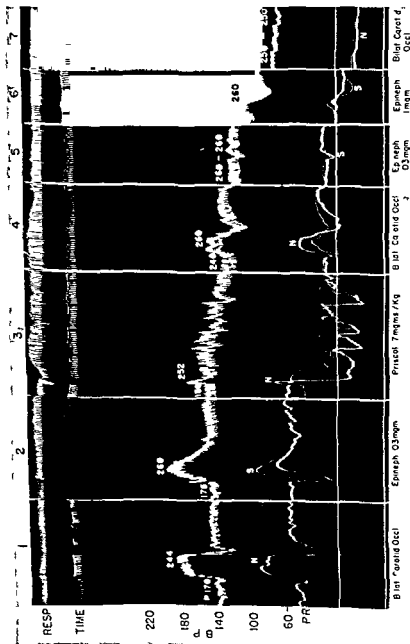


Fig 1.—Effect of occlusion of both carotid arteries and of intravenous injection of 0.3 mg of epinephrine upon respiration, mean systemic blood pressure and upon back pressure of a normally innervated limb (N) and of a sympathetomized limb (S) shown in Table 1 and 2. Administration of 1 mg of Priscol (7 mg per kilogram) and 2) produced increase of pulse rate and a gradual decrease of back pressure of the normal limb occurred. The four panels on the right demonstrate reduction of carotid sinus reflex block of response to epinephrine and finally a block of response to carotid occlusion. Bilateral carotid occlusion gradually reduced during the experiment.

one to two hours of experimental study and after reduction of mean systolic blood pressure to levels ranging from 50 to 74 mm Hg. Only one animal had complete block of the reflex at higher blood pressure levels. Mean systolic blood pressure, originally 130 mm Hg in this dog became 178 after 0.6 mg per kilogram, 160 after addition of 1.2 mg per kilogram, and 120 after another 3.6 mg per kilogram. Carotid sinus reflex was blocked at all levels as also subsequently when increased dosage had decreased the blood pressure.

Epinephrine—Before Priscol 0.03 to 0.05 mg of epinephrine administered intravenously to each of six dogs produced elevations of blood pressure ranging from 108 to 178 mm Hg in one and from 156 to 250 in another, and increases of pulse rate ranging between 156 to 196 and 176 and 260. After initial doses of Priscol as low as 0.03 to 0.07 mg per kilogram pressor responses to 0.3 and 0.5 mg of epinephrine were reduced, a typical change being from 110 to 150 mm Hg. After 1.8 to 11 mg per kilogram of Priscol doses of epinephrine varying from 0.01 to 0.1 mg per animal usually effected reduction of blood pressure (epinephrinal reversal) and rarely an increase. When increase occurred it was less than 16 mm Hg (Fig. 1). This response maintained whether or not mean systolic blood pressure had been reduced. Doses of epinephrine as high as 1 to 3 mg per dog also produced moderate lowering or only slight increase of blood pressure. Heart rate was accelerated by Priscol almost as much as by epinephrine. Hence epinephrine administered after Priscol caused little additional speeding of the heart. Examination of consecutive tests reveals that block or reversal of the usual pressor response to epinephrine occurred with doses of Priscol smaller than those required to produce reduction or block of carotid sinus and other reflexes. Also when single effective doses of Priscol were given (Fig. 1) block of pressor response to epinephrine occurred sooner than block of reflexes.

Pituitrin and Prostigmine—Ten and twenty units of Pituitrin, respectively were given to two dogs whose blood pressure had been markedly reduced by Priscol. Pressure rose from 56 to 78 mm Hg in one and from 22 to 94 mm Hg in the other. Carotid sinus reflexes remained blocked. Pressure was not changed or reflexes restored by 0.5 mg of Prostigmine.

Stimulation of the Central End of a Divided Vagus Nerve—The central end of either divided vagus was stimulated before Priscol in four dogs using a tetanizing current. This produced marked elevation of blood pressure and increase in heart rate. After 1.9 to 11.4 mg per kilogram of Priscol and after reduction of blood pressure similar stimulation produced rises ranging between 48 and 102 and 72 and 132 mm Hg. After 6.7 to 20.4 mg per kilogram and after further reduction of blood pressure elevation with central vagus stimulation was blocked.

Asphyxia—At the termination of five of these experiments and after large doses of Priscol blood pressure was reduced to 37 to 56 mm Hg by asphyxia.

Peripheral Resistance of Normal and Sympathectomized Hindlimbs Estimated by Wolf Method—Throughout these tests back pressures from the distal

ends of divided femoral arteries were recorded by mercury manometers to estimate peripheral resistance. A separate manometer was used in the proximal end of one artery to record systemic blood pressure. Peripheral resistance was estimated by relating changes of back pressure in the normal and the sympathectomized limb to those of systemic blood pressure. Before Priscol, back pressure of the normally innervated limb altered rapidly and actively in response to reflexes while that of the sympathectomized limb reflected changes of systemic blood pressure. Increases were usually less extensive than those of the normally innervated limb (Fig 1). Also before Priscol back pressure of the normally innervated limb responded to 0.03 mg of epinephrine usually first by decrease and then by increase whereas that of the sympathectomized limb promptly increased and reached levels somewhat exceeding the height reached by the normal limb.

Administration of initial doses of Priscol usually produced approximately equivalent changes in peripheral resistance of the normal and the sympathectomized limbs. Moderate differences when they appeared were in the direction of more prompt or extensive lowering of pressure in the normally innervated limb. Successive doses totaling 1.5 to 7 m_g per kilogram were required before reflex responses of normal and sympathectomized limbs became equal and passive.

Etamon

Blood Pressure and Pulse—Etamon 15 mg per kilogram administered intramuscularly in 3 dogs as an initial dose effected slow and moderate reduction of blood pressure and did not produce tachycardia. Etamon 3 mg per kilogram administered intravenously as an initial dose in the fourth animal produced prompt reduction of mean systolic blood pressure from 102 to 54 mm Hg and an increase of heart rate. Blood pressure recovered to 90 mm Hg within five minutes. With one exception subsequent intravenous injections produced similar transient lowering of pressure followed by gradual but incomplete recovery and subsequent intramuscular injections produced slow continued moderate reduction. The exception occurred in one animal following the initial administrations of Etamon. Consecutive intravenous injections of 5, 8, 8, 20 and 40 mg per kilogram in this animal produced increases of pressure the greatest being an increase from 110 to 190 after the 40 mg per kilogram dose. Pulse rates increased during these pressor responses and then again slowed. A typical increase was from 132 to 184. The 40 m_g dose was followed by respiratory failure and death.

Carotid Sinus Reflex—Before Etamon occlusion of both carotid arteries produced elevations of blood pressure ranging between 106 to 140 and 130 to 160 mm Hg. After initial doses of 15 mg per kilogram intramuscularly in three dogs responses during one half hour were reduced being between 60 to 80 and 110 to 128 mm Hg. After an initial dose of 3 mg per kilogram intravenously the reflex was blocked within three minutes. In all animals after the next injection occlusion of the carotid arteries produced no change of blood pressure (Fig 2). Pressures were 52, 80, 82 and 84 mm Hg at the time of the first complete block.

Epinephrine—Before Etamon 0.3 mg of epinephrine in three dogs elevated blood pressure from 100 to 180, 128 to 172, and from 102 to 170 mm Hg. The fourth dog required 0.1 mg. to elevate pressure from 124 to 186 mm Hg. After initial and subsequent doses of 1 Etamon the response to the same dose of epinephrine was equal in two animals and definitely accentuated in two (Fig. 2) since the rise occurred from lower pressure levels, 64 to 154 and 60 to 182 mm Hg.

Prostigmine—Prostigmine in amounts of 0.5 mg. was administered intravenously to three dogs after cumulative total doses of Etamon ranging from 9 to 35 mg. per kilogram had effected reduction of blood pressure and block of carotid sinus reflex. Blood pressures rose after Prostigmine in the three animals from 62 to 82, 40 to 84, and 52 to 94 mm Hg respectively. Also after this and subsequent larger doses of Prostigmine carotid sinus reflexes became active although not equal to those before Etamon.

Stimulation of the Central End of a Divided Vagus Nerve—Stimulation of the proximal end of one divided vagus nerve in three dogs before Etamon produced marked elevation of pressure and acceleration of heart rate. After initial and subsequent injections of 1 Etamon increase of blood pressure and increase of heart rate with stimulation were similar to that before the drug in two dogs and definitely blocked in one (Fig. 2).

Anoxia and Asphyxia—Anoxia produced by spontaneous respiration of 7 per cent O₂ in 93 per cent N₂ produced elevation of blood pressure before and after 15 mg. per kilogram of Etamon in one dog. Terminal asphyxia in another failed to elevate blood pressure.

Peripheral Resistance of Normal and Sympathectomized Hindlimbs Estimated by Wolf Method—Back pressure or peripheral resistance of normal and sympathectomized hindlimbs was recorded throughout this series of tests in three dogs. Active and passive responses to reflexes were obtained before Etamon. Also responses to epinephrine were biphasic in the normal leg and directly pressor in the sympathectomized limb. After effective doses of Etamon, carotid sinus reflexes were blocked and back pressure did not change during occlusion of the carotid arteries (Fig. 2). Stimulation of the central end of a divided vagus nerve usually elicited active and passive responses of back pressure lower however than those before the drug. Epinephrine after Etamon usually produced equal and active responses in the normally innervated limb and in the sympathectomized limb.

Stimulation of the Peripheral End of a Divided Vagus Nerve—Before Etamon stimulation of the peripheral end of the divided left vagus produced slowing of heart rate and reduction of blood pressure. After 21 to 25 mg. of Etamon this response was blocked; stimulation by tetanizing current producing no obvious effect.

Dibenamine

Blood Pressure and Pulse—Initial doses of Dibenamine (5 mg. per kilogram) were administered intravenously to each of four dogs. This dose produced no change of blood pressure during fifteen minutes in one animal and a gradual decline in three (Fig. 3). Pulse rate changed little. Subsequent injec-

tion of 5 mg per kilogram in each gradually hastened the decline of blood pressure and after one half to one hour systemic blood pressure ranged from 40 to 64 mm Hg.

Carotid Sinus Reflex—Before Dibenamine carotid sinus reflexes were active in four dogs increases of blood pressure ranging between 106 to 140 and 125 to 204 mm Hg. After initial injection of 5 mg per kilogram reflexes were abolished in three animals at blood pressure levels of 60, 70, and 76 mm Hg (Fig

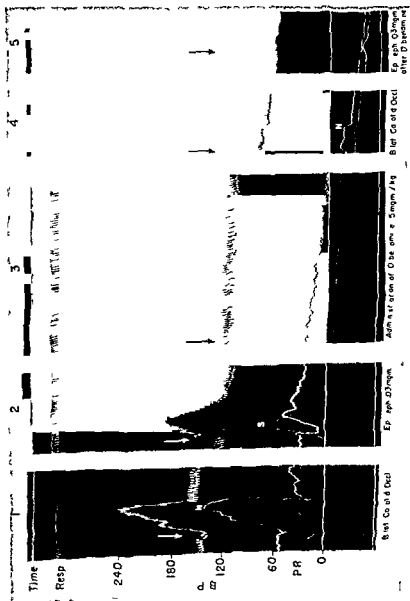


Fig. 3.—Left: arterial occlusion of carotid arteries and injection of epinephrine are again shown on the left. Intravenous administration of Dibenamine (5 mg per kilogram) affected slow gradual decline of systemic blood pressure (black line) and reflexly administered line b (lan 1, 2). One hour later (P. N. 1, 4) blood pressure was again fully reduced and carotid sinus reflexes at 1 block. 1. By ascorbic acid to epinephrine (lan 1, 5) & blocked.

3) The fourth dog had a blood pressure of 96 after an initial 5 mg per kilogram and it increased to 144 mm Hg during carotid occlusion. After another 5 mg per kilogram the response in this animal was 72 to 100 mm Hg. Subsequently and without more of the drug, responses ceased.

Epinephrine—Before Dibenamine, 03 mg epinephrine produced elevations of blood pressure ranging between 120 to 192 and 104 to 212 mm Hg. Soon after the initial dose of Dibenamine the pressor response to the same dose of epinephrine was blocked in one animal (Fig. 3), reduced in two (68 to 104 and 58 to 96 mm Hg), and equal to that before Dibenamine in the fourth (110 to 176 mm Hg). Following subsequent injections of Dibenamine administration of epinephrine produced neither rise nor fall of systemic blood pressure.

Pituitrin and Prostigmine—Twenty units of Pituitrin were administered intravenously to 3 dogs after total cumulative doses of Dibenamine of 10 to 20 mg per kilogram and after reduction of blood pressure with block of reflexes. Blood pressures rose from 32 to 70, 52 to 146 and 82 to 130 mm Hg respectively but reflexes were not restored. Prostigmine had no effect upon blood pressure or reflexes.

Stimulation of the Central End of a Divided Vagus Nerve—Only two animals were tested after Dibenamine. Blood pressure had been reduced to 38 and 54 mm Hg. Stimulation failed to increase pressure.

Asphyxia and Anoxia—At the termination of each experiment the trachea was obstructed producing death by asphyxia. Mean systolic blood pressure did not rise. Anoxia 7 per cent O_2 in 93 per cent N_2 produced some elevation of blood pressure before Dibenamine in one animal and failed to produce elevation after the drug.

Peripheral Resistance of Normal and Sympathectomized Hindlimbs Estimated by Volf Method—Before Dibenamine reflex changes of back pressure in the sympathectomized leg were passive and those of the normally innervated limb were active. After epinephrine responses were direct and diphasic respectively. Following initial and subsequent injections of Dibenamine responses to reflexes in the normally innervated limb became passive and response to epinephrine was blocked, back pressure not changing in either the sympathectomized or the normally innervated leg.

DISCUSSION

Sympatholytic properties of Priscoi, Etamon, and Dibenamine have in general been confirmed using techniques different from those described in the literature. Block of certain reflexes normally dependent upon the sympathetic nervous system does occur. Comparison of results of sympathetic block by drugs with previously reported results of total or lumbar sympathectomy in dogs indicates that the pharmacologic sympathectomy approaches effectiveness of actual sympathectomy. Back pressures of the normally innervated and the sympathectomized hindlimbs of a dog respond passively and equally to changes of systemic blood pressure produced by reflexes or drugs after effective doses of these three agents. Experiments have indicated however that pharmacologic blockade may vary from animal to animal and may fail to block strong pressor reflexes such as those produced by stimulation of the central end of a vagus nerve. Decrease or

cantly reduce systemic blood pressure altering reflexes produced by cold or by breath holding.¹² Similarly it does not significantly reduce blood pressure in the supine or erect position. Since it evidently requires 50 to 75 mg. per patient to increase circulation of extremities, 125 to 175 mg. to produce adrenalin blockade, and 150 to 200 mg. to block reflexes and reduce blood pressure, the therapeutic effect desired can be selected by regulating the dose. Thus far, amounts of more than 75 mg. have been employed only for test purposes. Apparently, Priscol alone of the three drugs studied has in a low dose range this ability to produce peripheral vasodilatation at a level below that necessary for adrenolysis or sympatholysis as judged by systemic arterial blood pressure responses.

Dibenzamine is similar to Priscol in its adrenolytic property and may be somewhat more effective as a systemic sympatholytic agent. Our clinical experience with this drug is limited. These experiments have indicated, however, that effective doses produce a gradual decline of blood pressure and that effects of the drug last many hours. Although prolonged action may be advantageous under certain circumstances, treatment of possible adverse reactions might be difficult in the absence of an effective antidote. Also although there is some evidence that the drug may be given by mouth, administration clinically has usually been limited to the intravenous route.

Use of Etamon for disorders or diseases of the circulation is limited by accessory effects produced by its general ganglionic blocking action. Examples are loss of accommodation of the eye, decrease or cessation of peristalsis throughout the alimentary tract and alteration of function of the urinary bladder. Such parasympathetic blocking side effects do not occur after the two adrenolytic and sympatholytic drugs with which different or characteristic side effects occur. Etamon is not adrenolytic. Reduction of blood pressure occurs promptly after intravenous administration of amounts necessary to produce sympatholytic or parasympatholytic effects. Abrupt reduction of blood pressure may not be desirable particularly at the cerebral or coronary arteries are markedly diseased.

Finally, these experiments would indicate that three useful drugs have been developed each capable of simulating effects of sympathetic block or actual sympathectomy.

CONCLUSIONS

- 1 A study of the actions of Priscol, Dibenzamine, and Etamon upon systemic and peripheral circulation by methods described has permitted comparison of effects of each drug with the others and with known effects of surgical sympathectomy.

- 2 A block of reflexes normally dependent upon the sympathetic nervous system, approaching that effected by actual sympathectomy, was achieved by each of these drugs.

- 3 Effects produced by any of the three drugs were occasionally irregular or variable, particularly with smaller doses.

- 4 Priscol and Dibenzamine were found to be adrenolytic and sympatholytic agents. Pituitrin partially restored blood pressure reduced by these drugs.

block of the pressor response to this reflex usually occurs only after blood pressure has been reduced below shock levels. Block of the carotid sinus reflex occurs after less reduction of blood pressure.

Former experiments have indicated that reduction of blood pressure occurs during the first few months after total sympathectomy in dogs. This operation requires three operative procedures at intervals of several weeks following which blood pressures range from 80 to 100 mm of mercury. Transection of the low cervical spinal cord in dogs effects among other things interruption of central vasomotor tone simulating an acute sympathectomy. Following cord section blood pressure is reduced to values around 70 to 80 mm. Either complete sympathectomy or division of the cord interrupts the carotid sinus reflex, the pressor response to stimulation of central end of the divided vagus and increase of pressure with anoxia. The three drugs studied in proper doses produced comparable reduction of blood pressure and block of the carotid sinus reflex. Increased amounts of the drugs further reduced blood pressure to definite shock levels. Block of the pressor responses to anoxia and to stimulation of the central end of a divided vagus then occurred.

Experiments have indicated that two of the three drugs studied are similar in some respects. These Priscol and Dibenamine block or reverse the blood pressure elevating action of epinephrine. They cause reduction of blood pressure which can be partially restored by pituitrin. The third drug Etamon is different in that it does not block epinephrine and blood pressure reduction is restored by prostigmine and not pituitrin. Prostigmine is apparently a good antidote in that restoration of blood pressure and recovery of autonomic reflexes occur.

Other differences between the three drugs will be discussed. Initial or subsequent injections of each usually reduced blood pressure. Occasionally however injections produced transient elevations. Increases were most frequent after Priscol. Also increase of pulse rate was more frequent and persistent after Priscol. Nevertheless certain possible advantages of this drug were observed. Fall of pressure with Priscol occurred promptly with large doses and could be easily regulated by gradually increasing the total dose. The fall after effective doses of Dibenamine occurred only slowly and continued progressively lower for several hours. That after Etamon was abrupt and tended to be more transient. Also although accurate measurements were not obtained an increase of redness of the skin or occurrence of a peripheral cutaneous flush occurred after Priscol. This was obviously more intense than any changes effected by alteration of circulation through the skin after Dibenamine or Etamon. This effect together with block of the pressor response to epinephrine could be obtained without marked reduction of blood pressure by employing graduated doses of Priscol.

From the clinical point of view therefore Priscol seems to be the most easily administered and regulated of the three drugs. Our detailed clinical experience has been limited to this preparation. It is of interest that 50 to 75 mg increase of the pulse is not sufficient to cause a significant increase of the pulse rate. This increase does not signify

THE RELATIONSHIP OF GASTRIC ACIDITY TO GASTRIC AND EXTRAGASTRIC NEOPLASMS

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INTRODUCTION

THE association of achlorhydria and hypochlorhydria with gastric carcinoma is a fact that has been noted by many observers¹⁻⁶ and has been stressed in the diagnosis of gastric cancer. Little information, however, is available on the relationship between gastric acidity and extragastric malignancies. This information is obviously of great importance for it would reveal whether consistently reduced gastric acidity is associated only with gastric malignancies or whether it is a manifestation of reduced function of the parietal cells in the glands of the gastric mucosa due to toxic systemic effects of any malignancy.

It was the purpose of this study to investigate the relationship between gastric acidity and extragastric malignancies.

REVIEW OF LITERATURE

In 1880, Fenwick described marked atrophy of gastric mucosa in a group of patients with extragastric malignancies. In his group were included 16 patients with carcinoma of the breast, 2 with cancer of the rectum and 1 with carcinoma of the bladder, penis and groin (metastases); no gastric acid determinations were made, however. Fwald⁷ in 1886 reported 1 patient with carcinoma of the duodenum, 2 cm. below the pylorus who had gastric anacidity and gastric mucosal atrophy. Riegel⁸ in 1886 observed lowered gastric acidity in a case of carcinoma of the esophagus. Moore, Alexander, Kelly, and Roaf⁹ in 1905 found that there was reduced acidity or complete gastric anacidity in 17 cases of extragastric malignancies and concluded that achlorhydria which is associated with gastric malignancy is not due to the local effect of tumor on the gastric mucosa because it was present in malignancies other than the stomach. Friedenwald and his co-workers^{11, 12} investigated this problem twice, once in 1907 and again in 1927. In the later study using the fractional meal as a gastric acid stimulant they investigated 38 patients with various extragastric malignancies and found achlorhydria in 37 per cent and hypochlorhydria (less than 30° free acid) in an additional 18 per cent. This lowered gastric acidity persisted even after the removal of the malignancy by surgery. In 1939 Neehles and co-workers¹³ showed experimentally that the gastric acidity in rabbits was not altered in the presence of diffuse extragastric carcinomatosis produced by the inoculation of the very malignant Brown Pearce rabbit carcinoma.

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5 Etamon behaved as a ganglionic blocking agent and was not adrenergic. Prostigmine restored blood pressure reduced by this drug and also of reflexes which it has blocked

REFERENCES

- 1 Grimson K S Sympathectomy and the Circulation. *Anatomic and Physiological Considerations and Early and Late Limitations*. *Circulation* 19: 277-298 1946
- 2 Southwick, R H The Surgical Treatment of Continued Hypertension. Some Thoughts About the Selection of Cases for this Form of Therapy, *J M Soc New J* 304 1947
- 3 Grimson K S The Surgical Treatment of Hypertension, *Advances Int Med* 2: 1947
- 4 Ahlquist R P Huggins R A and Woolbury R A The Pharmacology of Imidazoline (Iriscol) *J Pharmacol & Exper Therap* 89: 271-288 1947
- 5 Acheson G H, and Hendrix J P The Effect of Tetraethylammonium Ion on the Superior Cervical Ganglion of the Cat *J Pharmacol & Exper Therap* 6: 1946
- 6 Acheson G H, and Hendrix J P The Effect of Tetraethylammonium Ion on the Superior Cervical Ganglion of the Cat *J Pharmacol & Exper Therap* 6: 1946
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- 9 Acheson G H, and Hendrix J P The Effect of Tetraethylammonium Ion on the Superior Cervical Ganglion of the Cat *J Pharmacol & Exper Therap* 6: 1946
- 10 Acheson G H, and Hendrix J P The Effect of Tetraethylammonium Ion on the Superior Cervical Ganglion of the Cat *J Pharmacol & Exper Therap* 6: 1946
- 11 Acheson G H, and Hendrix J P The Effect of Tetraethylammonium Ion on the Superior Cervical Ganglion of the Cat *J Pharmacol & Exper Therap* 6: 1946
- 12 Acheson G H, and Hendrix J P The Effect of Tetraethylammonium Ion on the Superior Cervical Ganglion of the Cat *J Pharmacol & Exper Therap* 6: 1946
- 13 Ahlquist R P and Woolbury R A The Influence of Benzylimidazoline (Iriscol) on Sympathetic Vasoconstrictors and Vasodilators *Federation Proc* 5: 1946
- 14 Ahlquist R P Huggins R A and Woolbury R A The Pharmacology of Imidazoline (Iriscol) *J Pharmacol & Exper Therap* 89: 271-288 1947
- 15 Grimson K S Reardon M J Marzoni F A and Hendrix J P The Effect of Benzylimidazoline (Iriscol) on Vascular Diseases and Hypertension *Federation Proc* 6: 1947
- 16 Grimson K S Reardon M J Marzoni F A and Hendrix J P The Effect of Benzylimidazoline (Iriscol) on Vascular Diseases and Hypertension *Federation Proc* 6: 1947
- 17 Acheson G H, and Hendrix J P The Effect of Tetraethylammonium Ion on the Superior Cervical Ganglion of the Cat *J Pharmacol & Exper Therap* 6: 1946
- 18 Acheson G H, and Hendrix J P The Effect of Tetraethylammonium Ion on the Superior Cervical Ganglion of the Cat *J Pharmacol & Exper Therap* 6: 1946
- 19 Acheson G H, and Hendrix J P The Effect of Tetraethylammonium Ion on the Superior Cervical Ganglion of the Cat *J Pharmacol & Exper Therap* 6: 1946
- 20 Acheson G H, and Hendrix J P The Effect of Tetraethylammonium Ion on the Superior Cervical Ganglion of the Cat *J Pharmacol & Exper Therap* 6: 1946
- 21 Acheson G H, and Hendrix J P The Effect of Tetraethylammonium Ion on the Superior Cervical Ganglion of the Cat *J Pharmacol & Exper Therap* 6: 1946
- 22 Marzoni F A Reardon M J Hendrix J P Effects of Benzylimidazoline (Iriscol) in Partially Sympathectomized Dogs *Federation Proc* 6: 1947
- 23 Reardon M J Marzoni F A Hendrix J P and Grimson K S Effects of Benzylimidazoline (Iriscol) on Vascular Reflexes and Peripheral Resistance in Dogs and Man *Bull Am Coll Surg* 32: 1947
- 24 Marzoni F A Reardon M J Hendrix J P and Grimson K S Effects of Benzylimidazoline (Iriscol) on Vascular Reflexes and Peripheral Resistance in Dogs and Man *Bull Am Coll Surg* 32: 1947
- 25 Hendrix J P Reardon M J and Marzoni F A Observations on the Effect of Benzylimidazoline (Iriscol) in Man *Federation Proc* 6: 1947

TABLE II GASTRIC ACIDITY IN PATIENTS WITH MALIGNANT EXTRAGASTRIC TUMORS

TUMOR	ORGAN	ACHLOP HYDRIA (0)	HYPO CHLOP HYDRIA (1 to 9)	NORMAL ACIDITY (30 to 49)	HYPERTHLOP HYDRIA (50 or more)	TOTAL
Carcinoma	Colon	3	-	3	4	10
Carcinoma	Cecum	-	-	5	1	10
Carcinoma	Rectum	3	5	2	4	14
Carcinoma	Esophagus	2	4	2	0	8
Carcinoma	Tongue	3	1	1	3	8
Carcinoma	Arrestate	11	9	7	3	30
Carcinoma	Bladder	1	3	-	3	9
Carcinoma	Breast	13	3	6	3	29
Carcinoma	Bronchus	3	-	1	1	7
Carcinoma	Larynx	2	2	1	1	6
Carcinoma	Cervix uteri	3	-	-	-	9
Carcinoma	Skin	17	12	14	10	49
Carcinoma	Anus	0	0	0	1	1
Carcinoma	Pancreas	1	1	0	0	2
Carcinoma	Kidney	1	1	0	1	3
Carcinoma	Gall bladder	1	0	0	0	1
Carcinoma	Thyroid	1	0	-	0	3
Carcinoma	Parotid	0	1	0	0	1
Carcinoma	Jejunum	0	1	0	0	1
Carcinoma	Rectum	0	0	1	0	1
Lymphoblastoma	Tongue	0	1	0	0	1
Lymphatic leucemia	-----	3	2	-	1	6
Hodgkin's disease	-----	0	0	0	1	1
Lymphosarcoma	Tonsillar area	0	0	0	1	1
Lymphosarcoma	Lymph gland	1	1	0	0	2
Osteogenic sarcoma	Tibia and sternum	0	0	1	1	2
Chondro sarcoma	Pelvis	0	0	0	1	1
Fibro sarcoma	Leg and back	0	-	2	0	4
Malignant melanoma	--	2	0	3	1	6
Myelogenous leucemia	--	3	1	0	0	4
Total		80	60	50	45	144
Total (percentage)		55	42	35	31	100

of achlorhydria and hypochlorhydria for each of the group may not be significant but for the total group of malignant and benign extragastric tumors the statistical data are valid. The incidence of achlorhydria hypochlorhydria normal gastric acidity and hyperchlorhydria for this group of extragastric malignant tumors as a whole is given in Table III. It can be seen that 80 (32.9 per cent) of the patients were achlorhydric 60 (24.6 per cent) were hypochlorhydric 50 (24.2 per cent) had normal gastric acidity and 45 (18.4 per cent) had hyperchlorhydria. The average age of the group was 64 years. Forty eight per cent were female and 52 per cent were male.

TABLE III GASTRIC ACIDITY IN MALIGNANT EXTRAGASTRIC TUMORS

DEGREES OF FREE HCl	NO	PER CENT	AV AGE (YEARS)	FEMALE	PER CENT	MALE	PER CENT
Achlorhydria (0)	80	55	64	41	32	39	48
Hypochlorhydria (1 to 9)	60	42	63	-	45	31	35
Normal (30-49)	50	35	63	30	30	29	50
Hyperchlorhydria (50 or more)	45	31	66	20	46	15	54
Total	144	100	64	114	48	16	52

MATERIAL AND METHODS

All patients over the age of 50 years registering at the outpatient clinics of the University Hospitals for the first time were subjected to a gastric analysis employing three successive doses of 0.5 mg. of histamine, given hypodermically as a stimulant to gastric secretion. Topfer's reagent was used to test for free hydrochloric acid, and quantitative estimations were made using $\frac{N}{10}$ NaOH and Topfer's reagent as the indicator. In a number of instances the patients for one reason or another were not given the three conventional doses of histamine but they did receive one or two injections of histamine and these patients were included in our statistical data. Patients not receiving histamine were excluded from the study. Patients who had no free hydrochloric acid after histamine stimulation were considered to be achlorhydric. Those who had free hydrochloric acid following histamine stimulation were further subdivided into the following groups:

- (a) Hypochlorhydria—maximum free hydrochloric acid not exceeding 29°
- (b) Normal acidity—free acid ranging between 30 and 49°
- (c) Hyperchlorhydria—free acid exceeding 50°

The diagnosis of the tumors was based on microscopic examination of a section taken from a biopsy or from the tumor itself after excision.

OBSERVATIONS

In all 1,315 patients over the age of 50 years had gastric analyses using histamine as the gastric acid stimulant. Of this group (Table I) 906 patients did not have tumors either malignant or benign. Of the 409 patients with neoplasms 337 had extragastric tumors and the remaining 72 had tumors of the stomach.

TABLE I. INCIDENCE OF NEOPLASTIC AND NON-NEOPLASTIC DISEASES IN PATIENTS EXAMINED

	NO.	PER CENT OF TOTAL
Neoplastic Diseases	409	31
I Extragastric	337	82.4
(a) Malignant	244	59.3
(b) Benign	93	22.7
II Gastric	72	17.6
(a) Carcinoma	57	13.8
(b) Benign	15	3.7
Non neoplastic Diseases	906	69.1
Total	1315	100

Extragastric Tumors.—Table I indicates that of the 337 patients with extragastric tumors 244 had malignant and 93 benign neoplasms.

Malignant Extragastric Neoplasms.—

Table II presents the types of neoplasms, the organs affected and the varying degrees of gastric acidity found in the groups of malignant extragastric tumors. In the main the number of tumors in each organ is small, ranging from 1 to 49, so that from the statistical point of view the presence or absence

In the various subdivisions of the benign and malignant extragastric tumors where there were at least 4 patients the only marked variation in the incidence of achlorhydria and hypochlorhydria, from the group as a whole occurred in the patients with myelogenous leucemia where the incidence of achlorhydria was 75 per cent and hypochlorhydria 25 per cent and in polyposis of the colon where the incidence of achlorhydria was 0 (Table VI). However the number of cases in each of these subdivisions was small (4 patients with myelogenous leucemia and 8 patients with colonic polyposis).

Gastric Neoplasms —

Gastric carcinoma In this study (Table VII) there were 57 patients with gastric carcinoma. In this group the incidence of achlorhydria, hypochlorhydria, normal gastric acidity and hyperchlorhydria were, respectively 85 per cent, 5 per cent, 5 per cent, and 5 per cent. The average age of the group was 62 years and 23 per cent were female and 77 per cent were male.

TABLE VII GASTRIC ACIDITY IN CARCINOMA OF THE STOMACH

	ACHLORHYDRIA		HYPOCHLORHYDRIA		NORMAL GASTRIC ACIDITY		HYPERCHLORHYDRIA	
	PER	AGE	PER	AGE	PER	AGE	PER	AGE
(more)								
Total	57	100	6	13	43	44	77	

Benign Gastric Neoplasms—In the benign gastric neoplasms (Table VIII) there were 13 patients with gastric polyps, all of which had achlorhydria and 2 patients with leiomyoma, one of which had achlorhydria and one hyperchlorhydria. The average age for patients with polyps and leiomyomas was 61 years, and 8 of them (54 per cent) were male and 7 (46 per cent) were female.

TABLE VIII GASTRIC ACIDITY IN BENIGN GASTRIC TUMORS

DEGREES OF ABNORMALITY	POLYPS		LEIOMYOMAS	
	NO	PER CENT	NO	PER CENT
Achlorhydria (0)	13	100	1	50
Hypochlorhydria (1 to 29)	0	0	0	0
Normal (30 to 49)	0	0	0	0
Hyperchlorhydria (50 or more)	0	0	1	50
Total	13	100	2	100

Males and 6 females
(Male and 1 female
Average age 61 years.

DISCUSSION

From this study it is evident that the incidence of achlorhydria is high in gastric neoplasms. Eighty-five per cent of the patients with gastric carcinoma had achlorhydria and an additional 5 per cent had hypochlorhydria. Thus 90 per cent of all patients with cancer of the stomach had either achlorhydria or hypochlorhydria. These results correspond closely to those reported by Hebbel and Gavisar.¹¹ They found in 175 cases of gastric carcinoma

TABLE IV EXTRAGASTRIC MALIGNANCIES

NEOPLASM	AVERAGE AGE (YEARS)	ACHILORHYDRIA (PER CENT)	HYPOCHLORHYDRIA (PER CENT)
Carcinoma skin	60	26	4
Carcinoma, colon and rectum	57	31	20
Carcinoma, prostate	73	37	30
Carcinoma breast	59	45	17

The most common form of extragastric malignancies found were of the skin (49 patients), the colon and rectum (46 patients), prostate (30 patients), and breast (29 patients). The incidence of achlorhydria and hypochlorhydria in each of these groups was as shown in Table IV.

Benign Extragastric Neoplasms—In the benign extragastric tumor group (Table V) 30 per cent of the patients had achlorhydria 28 per cent had hypochlorhydria 20 per cent had normal gastric acidity and 22 per cent had hyperchlorhydria the average age was 64.7 years and 45 per cent were female and 55 per cent were male. The types of benign extragastric neoplasms are given in Table VI.

TABLE V GASTRIC ACIDITY IN BENIGN EXTRAGASTRIC TUMORS

DEGREES OF FREE HCL	NO	PER CENT	AGE (YEARS)	FEMALE	PER CENT	MALE	PER CENT
Achlorhydria (0)	28	30	64	13	41	15	53
Hypochlorhydria (1 to 9)	26	28	63	9	35	11	50
Normal (30 to 49)	18	20	63.9	9	50	9	50
Hyperchlorhydria (50) or more	21	22	66	10	50	11	50
Total	93	100	64	41	45	55	55

TABLE VI GASTRIC ACIDITY IN PATIENTS WITH BENIGN EXTRAGASTRIC TUMORS

TUMOR	ORGAN	ACHILORHYDRIA (0)	HYPOCHLORHYDRIA (1 TO 9)	NORMAL ACIDITY (30 TO 49)	HYPERCHLORHYDRIA (50 OR MORE)	TOTAL
Adenoma	Thyroid	9	7	4	4	24
Polypoid	Large bowel	0	3	4	1	8
Benign tumor	Skin and subcutaneous tissues	6	5	3	4	18
Lipoma fibroma dermoid and sebaceous cyst, neurofibroma melanoma etc						
Fibroid and polyp	Uterus	4	5	1	3	14
Cysts and fibromas	Ovaries	2	1	2	5	10
Astrocytoma	Brain	2	1	0	1	4
Cyst	Maxilla	1	1	0	1	3
Mixed tumor	Parotid	0	1	0	0	1
Adenoma	Adrenal	0	0	0	1	1
Adenoma	Intestine	1	1	0	0	3
Lipilloma	Bladder (urinary)	1	0	0	0	1
Benign melanoma	Chondroid	0	0	0	1	1
Chondroma	Metatarsal bone	1	0	0	0	1
Hemangioma	Vertebra	0	0	2	0	2
Dermoid cyst	Melanin tumor	0	0	2	0	2
Total		30	28	20	21	100
Total (percent age)						

TABLE X FREQUENCY OF DEGREES OF GASTRIC ACIDITY IN DISEASE GROUPS
 (Percentage of total for groups given in parentheses)

DISEASE	DEGREES OF ACIDITY								TOTAL	
	0		1 to 2		30 to 49		50 or more			
	NO	PER CENT	NO	PER CENT	NO	PER CENT	NO	PER CENT	NO	PER CENT
1 Non neoplastic Extragastric Tumors	37	36	10	10	13	13	10	10	60	60
(a) Benign	25	70	26	28	18	20	21	22	90	71
(b) Malignant	80	78	10	16	29	24	45	18	144	183
3 Gastric Tumors										
(a) Carcinoma	48	85	7	5	7	5	3	5	57	45
(b) Polyp	13		0		0		0		13	1
(c) Leiomyoma	1		0		0		1		2	1
Total	177	100	53	30	57	32	70	39	257	100

If the disease groups 1 and 2 are treated as a unit and examined statistically for uniformity in degrees of achlorhydria it is found that the small differences in the percentages are well within the chance errors of sampling ($\chi^2 = 4.97$, $P = 6\%$). When the gastric carcinomas (group 3) are added however the frequency distributions become markedly heterogeneous because of this addition as evidenced by χ^2 rising to 61.4 and the probability of the deviations from homogeneity arising from chance factors alone falling to much less than one in a million. It is therefore clear that the predominance of achlorhydria among patients with gastric carcinomas is associated with this disease grouping in contrast with the other disease groupings. The remaining gastric neoplasms are too few in number to warrant their inclusion separately in this analysis.

validity of the contention that the incidence of achlorhydria and hypochlorhydria is significantly greater in patients with gastric carcinoma than in patients with extragastric malignancies or non neoplastic disease for the same age group

SUMMARY AND CONCLUSIONS

1 One thousand three hundred fifteen patients over the age of 50 years have been studied with respect to gastric acidity following the injection of histamine as a gastric acid stimulant

2 Two hundred forty four patients had malignant extragastric lesions and the incidence of achlorhydria and hypochlorhydria in this group was 32.8 per cent and 24.6 per cent respectively

3 The incidence of achlorhydria and hypochlorhydria in 93 patients with benign extragastric tumors was 30 per cent and 28 per cent respectively

4 Achlorhydria and hypochlorhydria occurred in 36 per cent and 23 per cent respectively of 906 patients with non neoplastic disease

5 Of 57 patients with gastric carcinoma 85 per cent were achlorhydric and an additional 5 per cent were hypochlorhydric

6 Thirteen patients with gastric polyps all had achlorhydria while of 2 patients with leiomyoma of the stomach one had achlorhydria and the other hypochlorhydria

7 Achlorhydria and hypochlorhydria occurs significantly more frequently in patients with cancer of the stomach than in patients with extragastric malignancies. The incidence of achlorhydria and hypochlorhydria of the latter group is practically the same as for the individuals with non neoplastic disease of the same age group

that the incidence of achlorhydria and hypochlorhydria were respectively 63 per cent and 17 per cent.

In benign polyps of the stomach (Table VIII) the incidence of achlorhydria was 100 per cent. This observation has been noted by others¹ and whether this represents a cause or an effect of the polyp is still a matter of debate. It is extremely interesting to note that a polyp even the size of a pea is associated with achlorhydria even after stimulation with three doses of $\frac{1}{2}$ mg. of histamine.

Leiomyomas of the stomach (Table VIII) are not regularly associated with achlorhydria or hyperchlorhydria as in the case of gastric polyps. In this study of the two leiomyomas of the stomach one was associated with achlorhydria while the other was associated with hyperchlorhydria.

The incidence of achlorhydria and hypochlorhydria is not as great in the patients with malignant extragastric tumors as compared with the individuals with gastric carcinoma. The incidence of achlorhydria and hypochlorhydria in the former group was 32.5 per cent and 24.6 per cent respectively. These figures correspond quite closely to the incidence of achlorhydria and hypochlorhydria in a group of patients of the same age group with non-neoplastic diseases, where 36 per cent of the patients were achlorhydric and an additional 23 per cent were hypochlorhydric (Table IX).

TABLE IX. GASTRIC ACIDITY IN NON-NEOPLASTIC DISEASES

DIFFERENCES OF FREE HCl	AGE	PER CENT
Achlorhydria (0)		60
Hypochlorhydria (1 to 29)		59
Normal (30 to 49)		59
Hyperchlorhydria (50 or more)		60
Total		59

It is thus apparent from these data that the incidence of achlorhydria and hypochlorhydria in patients with extragastric malignancy is about the same as for individuals without neoplasms and probably represents the incidence of achlorhydria and hypochlorhydria after histamine stimulation for the population of the same age group¹⁸ (average age 63.2 years) (Table X). The incidence of achlorhydria and hypochlorhydria in patients with gastric malignancies however is definitely increased in a significant manner over the average for the same age group. It is well known that age has a definite influence on gastric acidity. Luzzant and co-workers¹⁹ have shown that there is increase in the incidence of achlorhydria with increase of age and a definite and a swift rise in the frequency of achlorhydria in the age groups over 40 years. In this study the possibility of difference in the incidence of achlorhydria and hypochlorhydria in the groups with extragastric and gastric malignancies being due to difference in age levels can be dismissed for from Tables III, V, VII, VIII it can be readily seen that the average age for people with extragastric neoplasms (both benign and malignant) is practically the same as for the patients with gastric neoplasms. These facts establish the

TABLE X. FREQUENCY OF DEGREES OF GASTRIC ACIDITY IN DISEASE GROUPS
(Percentage of total for groups given in parentheses)

DISEASE	DEGREES OF ACIDITY								TOTAL	
	0		1 to 29		30 to 49		50 or more			
	NO	PER CENT	NO	PER CENT	NO	PER CENT	NO	PER CENT	NO	PER CENT
1 Non neoplastic	37	36	10	23	19	24	150	165	906	61
2 Extragastric Tumors										
(a) Benign	28	0	26	28	18	20	21	22	97	71
(b) Malignant	80	25	60	46	59	42	45	184	244	183
3 Gastric Tumors										
(a) Carcinoma	48	83		0		5	3	5	57	45
(b) Polyp	13		0		0		0		13	1
(c) Leiomyoma	1		0		0		1		2	1
Total	417	38	230	22	291	22	220	168	1310	100

If the disease groups 1 and 2 are treated as a unit and examined statistically for uniformity in degrees of chlorhydria it is found that the small differences in the percentages are well within the chance errors of sampling ($\chi^2 = 4.97$, $P = .67$). When the gastric carcinomas (group 3) are added however the frequency distributions become markedly heterogeneous because of this addition as evidenced by χ^2 rising to 61.8 and the probability of the deviations from homogeneity arising from chance factors alone falling to much less than one in a million. It is therefore clear that the predominance of achlorhydria among patients with gastric carcinomas is associated with this disease grouping in contrast with the other disease groupings. The remaining gastric neoplasms are too few in number to warrant their inclusion separately in this analysis.

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8 The validity of the use of achlorhydria and hypochlorhydria as signs in the diagnosis of gastric carcinoma is established in this study

REFERENCES

- 1 Van de Velden Ueber Vorkommen und Mangel der freien Salzsäure im Magensaft bei Gastrektasie, Deutsches Arch f klin Med 23 Jg 1891
- 2 Einhorn M Diseases of Stomach, ed 4 Baltimore 1896, William Wood & Company page 3-6
- 3 1894 page 491 in Relation to Disease New
- ritus Associated With Gastric
- itions on
- Organs,
- salzsäure
- secretion Uleus carcinomatosum duodeni Berl klin Wchnschr 23 Jg 1896
- 9 Riegel Zeitschr Beiträge zur Lehre von den Störungen der Saft secretion des Magens Klin med Berlin 11 1 1896
- 10 Moore B Alexander W, Kelly R L, and Roaf H F On the Absence or Marked Diminution of Free Hydrochloric Acid in the Gastric Contents in Malignant Disease of Organs Other Than the Stomach, Lancet 1 11 0 1906

OSTEOMYELITIS CAUSED BY *SALMONELLA PARATYPHI* (*BACILLUS PARATYPHOSUS A*)

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PARATYPHOID osteomyelitis has long been regarded as a comparatively rare condition. Cases reported in the literature show that osteomyelitis from a paratyphoid B organism occurred eight times to one for paratyphoid A. Most of the cases reported in the literature have not been fatal. However certain cases, particularly in children may terminate fatally as those cases reported by Veal and McFetridge.¹ Seidenstein reported three cases that were not of the acute type but cases that appeared spontaneously without ever having shown other symptoms as an enteritis or other *Salmonella* infection. Primary infection of *Salmonella* was not recorded in any of the three cases. Roentgenograms that are reproduced in many of the articles give a picture of typical chronic osteomyelitis with more or less localized areas of destruction involving usually one or at most two bones. Jetter² however reported a case of multiple osteomyelitis complicating a paratyphoid fever which terminated fatally. The roentgenograms illustrated in his paper show considerable massive destruction of several bones of the body. This marked destruction has been noted in the following case report.

REPORT OF CASE

A 10 year old white girl was admitted to the hospital on Aug. 16, 1946, complaining of a terrific pain and swelling of the lower end of the left femur with involvement of the knee joint. She had a history of slipping and falling on July 4, 1946, following which she noted some pain in the left knee. Two days later she noted abdominal cramps and nausea with one or two episodes of vomiting and one of diarrhea. The next morning on the third day following the injury she developed severe pain in the left femur at the lower end. She was put to bed by her family and no definitive treatment was given until six weeks later when she was seen at her home with a temperature of 100° F. A large swelling appeared at the lower end of the femur involving the popliteal space so that she was unable to flex the knee and she maintained the knee in a comparatively neutral position so that it was as comfortable as possible. On August 17, a blood culture was taken and many gram positive diplococci were found. Treatment was started prior to the report of the blood culture with 20,000 units of penicillin being given every four hours day and night. The urine examination was negative. The blood count on August 17 was: 3,500,000 red cells, 69 per cent hemoglobin, 10,400 white cells, 34 per cent lymphocytes, 61 per cent neutrophils, 56 per cent filamented, 10 per cent nonfilamented. Roentgenograms at this time disclosed (see Fig. 1) marked destruction of the entire lower end of the femur with obvious new development of bone. The destruction continuing up the shaft to the middle portion of the shaft. There was what appeared to be a large mass of undetermined nature in the popliteal space.

In spite of the positive blood culture and the roentgenographic finding it was thought that this might be an osteogenic sarcoma with a secondary infection of an osteomyelitis. The temperature under penicillin receded from 100.4° F. down to daily swings of approximately one degree. Other doctors who saw the x-ray pictures in consultation concurred in the diagnosis of an acute osteomyelitis or the possibility of an osteogenic sarcoma. On August 20, operative exploration of the infected area was undertaken with a frozen section to determine the nature of the infected condition. Reparations were made for high amputa-

apparently recovered with considerable rapidity for a few days. The two days following the operative procedure the temperature went to 100.6 F. Following that the temperature remained from 99 to 99.6 F., never going entirely to normal.

On August 27, another blood culture was taken, the results of which were found to be more cocci in clump. On September 2 an additional blood culture was reported negative in twenty-four hours. On forty-eight hours gram-negative bacilli which were mobile were recovered. These were thought to be a contaminant so the blood culture was repeated. This blood culture also showed the gram-negative bacilli. They were traced down and found to be paratyphoid A by fermentation and biochemical reactions and by specific antiserum agglutinations. On September 12 the blood culture was repeated again because we could hardly believe our findings. Again the blood culture was positive for a gram-negative bacillus and again was proved to be paratyphoid A. On September 9, the cast was removed and the dressing changed with removal of the petrolatum gauze and the drains in the popliteal space.



tion should this have been an osteogenic sarcoma. The frozen section proved the condition to be that of an osteomyelitis with many sequestra and much early bone formation, this accounting for its appearance as an osteogenic sarcoma. Just posterior to the lower end of the femur was a large abscess about the size of a small grapefruit. This was filled with necrotic tissue, pus, and pieces of bone. The bone was saucerized widely and curetted out with large curettes. All of the material that could be easily removed was removed from the wound. A petroleum jelly pack was left in the femur and rubber drains were inserted into the large abscess in the popliteal space. The leg was then dressed with petrolatum gauze and placed in a plaster cast hip spine to afford complete immobilization.

A culture was taken from the left femur and no organisms were found on direct smear. However, the culture recovered many cocci in clumps after twenty-four hours; the cocci grew so profusely that they covered the culture medium completely.

Two whole blood transfusions were given—one the day of the operation and one the day following it—and penicillin was continued at 50,000 units every four hours. The patient



A

B

osteogenesis in many areas has been completely opened by the infection.

on Aug 14
the staff
staff has

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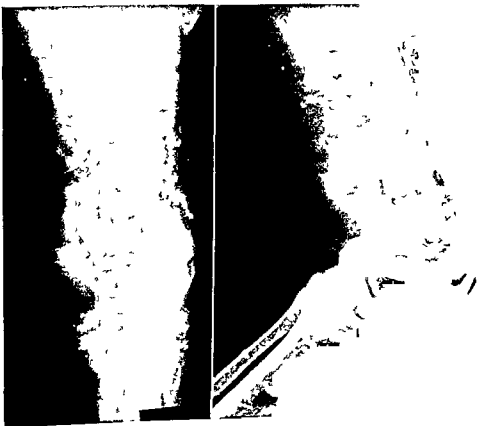
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A

B

this date another blood culture was taken and it was found to be negative for twenty four, forty eight and eighty two hours. The streptomycin however, was continued to complete the ten days' treatment. Before treatment was stopped there were more extensive eruptions on the arms, the chest, and the legs. There were no other symptoms of streptomycin sensitivity such as ringing of the ears, aphasia, vertigo, nausea or vomiting.

Repeated x ray views of the femur were made during the changes of the cast and it was found that there was no improvement in the roentgenograms until after the streptomycin therapy. By Feb 10, 1947 there was some filling in of the osteomyelitis defect and the texture of the bone appeared more solid. Further radiographic studies taken on May 16 and at three month intervals from that time on, show a continued improvement in the shaft of the left femur (see Fig. 2).

After one year's treatment in a plaster cast with complete immobilization the cast was removed and the child allowed up on crutches. The skin lesion had been healed completely at the time of cessation of streptomycin therapy. There was no additional infection either from gram negative or gram positive organisms following the thirty one days of penicillin and the ten days of streptomycin therapy. In August 1947 it was found that the left leg was shortened one and one half inches as compared with the length of the right leg. It was felt at this time that probably the epiphysis had been partially destroyed at the lower end of the femur especially the medial aspect of the femur. There was a 16 degree valgus deformity at the knee at this time. By October this had not improved and a lift with an elevated heel and sole was made for the left foot. This compensated for one half of the shortening and made her more comfortable and improved the gait. She was now allowed to walk on the leg with care and with the aid of crutches should she wish to make any long trip. A further check in December 1947 showed a great improvement in the length of the leg, a great improvement in the amount of calcium deposited in the affected area, and improvement in the valgus deformity at the knee.

In December the valgus deformity on the right leg (the good leg) was 6 degrees. The valgus deformity on the affected leg was 11 degrees, an improvement of 5 degrees over the measurements made in October 1947. The leg had grown in length so that it was but one inch shorter than the right leg. Radiographic examination at that time showed a femur that appeared almost within normal limits although evidences of the infection showed in the lower one half of the bone and in the roughness seen on both anterior and lateral views (Fig. 3).

DISCUSSION

It is generally considered that a mixed infection such as a coccal form and a bacillary form seldom if ever attack a bone simultaneously in a primary osteomyelitis. This I believe is a case of mixed infection in which there were two organisms involved in causing the primary lesion. It is probable that we would not have identified the two organisms were it not for the selective nature of penicillin in treating gram negative organisms. We were able to clear the gram positive organisms from the blood stream with the penicillin by its extended use for thirty one days. During all of this time there was no effect on the gram negative organisms which did not respond and which continually grew from all of the blood cultures in spite of the use of penicillin. The operative wound and the radiographic findings confirmed the presence of some additional infection other than the coccal form. The operative site did not heal or show evidences of healing under the use of the penicillin. It did show rapid closure and rapid healing after the streptomycin was used.

New gauze was placed in the wound and the plaster cast reapplied. Penicillin was continued all through this procedure. On September 18 penicillin was discontinued because it had no more effect on the gram negative organisms found in the blood stream. This was a total of thirty one days of penicillin therapy at the rate of 50 000 units every four hours.

Because we were able repeatedly to isolate this gram negative bacillus, paratyphoid A, we decided to use streptomycin which became available on September 20. The streptomycin was started on September 30 and given at the rate of 300 mg every three hours for ten days. This was considered as a very large dose for a child of 10 years; however, we felt that with a positive gram negative blood stream infection the maximum dose should be given. After eight days of treatment with streptomycin a fine papular rash developed on both arms. On



Fig. 3.—This is a view taken in December, 1941, showing an anteroposterior view of both the right and the left knee. This shows the final result there being a 5 per cent greater valgus deformity on the left knee as compared to the right knee. The child is now fully weight bearing and the end result of this marked osteomyelitis has been an adequately functioning knee rather than an amputated leg.

as paratyphoid A making the ratio of paratyphoid A osteomyelitis 1 to 6 for other *Salmonella* osteomyelitis cases. Any osteomyelitis caused by *Salmonella* infections can be considered an unusual occurrence.

CONCLUSION

Identification of the *Staphylococcus aureus* was made by repeated growth of the culture on plates. The organ maintained its characteristics of yellowish color and colony formation.

Identification of the paratyphoid A was done through fermentation reactions using first the fermentation of the carbohydrates dextrose, lactose, sucrose, maltose and mannitol. The results of these tests located this organ in the paratyphoid group. Further studies were made with Russell's media and Kiegl's media. The organ produced no change on the slant and produced a yellowish butt with gas formation in Kiegl's media.

Following these bacteriologic studies agglutination of the organism was done and it was found that there was positive agglutination with paratyphoid A in dilutions up to 1:60 and 1:20. There were no agglutinations with paratyphoid B agglutinins.

I should like to express my thanks to Dr. I. W. Meredith and Dr. D. W. Patter on for the radiographic work and to Dr. W. E. B. Hall for the laboratory and the pathologic work involved in this case.

REFERENCES

1. Veal J. B. and McFetridge E. M. Paratyphoid Osteomyelitis. Report of Two Cases. *Am J Surg* 43: 114, 117, 1929.
2. Weaver James B. and Sherwood Loraine. Hematogenous Osteomyelitis and Paratyphoid. Due to *Salmonella* *Suipetris*. reprinted from *J. A. M. A.* 105: 1148, 1151, 1930.
3. Rutter Henry H. and R. H. R. *New York State J. Surg* 29: 223, 1934.
4. Kulowski Jacob. *New York State J. Surg* 29: 223, 1934.
5. Kraus Ruth F. *New York State J. Surg* 29: 223, 1934.
6. Vinke Theodore H. and Downing Harold F. *Salmonella* Infection Involving the Knee Joint. *J. Bone & Joint Surg* 29: 232, 233, 1947.

According to Veal and McFetridge¹ the onset of a paratyphoid osteomyelitis, whether it is acute or subacute seldom has the same severity as that of a pyogenic infection. In view of this it is entirely possible that this case was primarily one of a paratyphoid A infection with a secondary coccus invasion of the bone when the patient's resistance had reached a low ebb. This child did not have a great deal of pain until after she had been disabled for about two weeks. Then she began having much more severe pain which would mark the time when the pyogenic infection invaded the osteolytic lesion.

This case demonstrates the excellent value of penicillin for gram positive organisms and of streptomycin for gram negative organisms. It must be remarked here that both penicillin and streptomycin should be used in adequate amounts. Many of the failures in therapy of osteomyelitis as in other conditions come from the fact that not enough of the bacterial inhibitors are used from the very first. Other failures are due to stopping the drug too soon. It is true that paratyphoid organisms are about as sensitive to streptomycin as any organism except tularemia. It is my feeling that the penicillin should be used in doses not smaller than 50,000 units every four hours in any case of severe infection. With the streptomycin I feel that it should be used to the patient's tolerance immediately, keeping a close watch on the sensitivity reactions especially ringing in the ears, vertigo, nausea and possible vomiting. Skin manifestations, similar to the ones seen in this case are of least importance while ringing of the ears is the most important indication for discontinuing its use.

This case also demonstrates the well known fact that osteomyelitis whatever the causative agent is still a very difficult disease to treat. This patient is making a good recovery and it is probable that the long extended immobilization had considerable value in maintaining the good work of the penicillin and the streptomycin. There is no reason in osteomyelitis to discontinue the use of open drainage, sequestration of the bone and packing with petrolatum gauze even though we have penicillin and streptomycin as very good bacteriostatic agents. It is probable that the blood transfusions given this child aided materially in controlling the more chronic gram negative infection of *Bacillus paratyphosus A*.

It is probable that there have been other cases of mixed infection in osteomyelitis. It was possible to identify both organisms because of the selective action of the therapeutic agents used. Usually the coccus forms obliterate all other growth on a culture. That was true early in this case. However with the history of enteritis for two days at the onset of this condition I feel that the primary cause was *Bacillus paratyphoid 1*. The reports in the literature concerning *Salmonella* infections causing osteomyelitis include the sixteen reported by Weaver, two by Veal and McFetridge, one by Jetté, three by Seidenstein, one by Krauss, a case of *Salmonella* infection involving the knee joint by Vinke and Downing, one by Gottehe, one by Kulowski, two by Ritter and Bochner, and one by Weaver and Sherwood making the total of twenty-eight cases. Of this group there are only four that have been definitely proved

The bowel movements which had previously numbered four to five per day, had decreased to one small one on the day previous to admission. At 2 A.M. on the day of admission the mother noted that the infant had passed a tarry stool with two or three bright red clots. At two- to three-hour intervals the infant seemed to have colicky pain lasting one to two minutes.

The child had been born following a normal pregnancy without complications. Labor was of ten hours' duration. Physiologic icterus was present for two weeks. Physical examination revealed a well-developed, well-nourished infant crying out as if in pain. The chest was clear and there were no abnormalities of the heart. The abdomen was slightly distended, somewhat rigid and tympanic. No definite masses could be felt. Bowel sounds were increased in pitch and frequency, suggestive of a mechanical obstruction. In the left inguinal area there was a firm, somewhat indurated mass which when palpated caused the infant to cry. Both testicles were in the scrotum.

On rectal examination a somewhat indurated mass could be felt just to the left of the midline. On removing the finger small fresh blood clots were noted.

Laboratory Data—The urine was normal. The hemoglobin was 13.4 Gm., the leucocytes numbered 15,000 per cmm. The plasma chlorides were 561.

The diagnosis at the time rested between a strangulated inguinal hernia and an intussusception.

X-ray Findings—A scout film of the abdomen revealed a rather marked distention of small bowel loops throughout most of the abdomen with no definite gas pattern recognized in colon loop. There was also considerable old fecal material mixed with gas, but it could not be determined whether this was in colon or small bowel. The appearance suggested a mechanical obstruction of the small bowel although the possibility of an ileus with impacted fecal material in the colon could not be excluded.

Barium Enema—Barium mixture was run into the colon under very low pressure and a collapsed colon of normal length and in normal position was filled. This examination demonstrated that the large collections of solid fecal material mixed with gas noted in these films were in the small bowel proximal to the colon. There was no evidence of intussusception.

Operation—With an intravenous needle in place the operation was begun about thirty-five hours after the initial attack. The initial incision paralleled the left inguinal ligament. It was our thought at the time to remove the mass and bowel in toto without entering the sac (Dennis and Varcoe). However in directing down through the skin around the mass the contents of the sac dropped back into the peritoneal cavity. An additional incision was then made extending from the middle of the initial incision horizontally and to the right. This was extended down to and into the peritoneal cavity.

When the peritoneal cavity was entered the bowel which was tremendously distended was visualized. This hampered the procedure tremendously and therefore an epitic decompression was performed. This was done first simply by tapping the bowel with a 15 gauge needle and then again by the method described by Wangensteen. This decompressed the bowel considerably and an attempt was made to replace the bowel within the abdomen. At this point difficulties with the anesthesia made it virtually impossible to do this. The pressure of the edges of the abdominal wound against the mesenteric vessels, especially the vein, caused considerable hematoma formation in part of the bowel which was of some worry but little consequence.

As soon as the anesthesia was readjusted the operation was continued. A quick examination of the bowel revealed a black gangrenous segment of about 10 cm. in length and located about 3 in. from the ileocecal junction. It was decided to perform an anastomosis of the ileum to the ascending colon after excising the involved ileum together with the cecum and appendix. An end-to-end epitic anastomosis of ileum to the ascending colon was made with one row of Lembert sutures. The mesenteries were then opposed and sutured together.

The inguinal hernia was then repaired simply by closing the neck of the sac from inside the abdomen. The abdominal wall was then closed with interrupted silk sutures.

Case Reports

PRIMARY RESECTION OF GANGRENOUS ILEUM WITH ANASTOMOSIS AND SURVIVAL IN A NINTYFN DAY OLD INFANT

A CASE REPORT

IVAN D BARONOFSKY, M D AND LLOYD NELSON M D , MINNEAPOLIS, MINN

(From the Departments of Surgery and Pediatrics University of Minnesota Hospitals)

THE management of strangulating gangrenous small bowel obstruction in early infancy has been a problem for many years. In their book Ladd and Gross¹ stated that in babies under 1 year of age, the mortality of resection for gangrenous intussusception runs extremely high averaging 75 per cent or more. In their series of eighteen cases wherein resection was combined with anastomosis, only three patients recovered. In congenital atresia of the intestine and colon, where successfully treated patients are still rarely described in the medical literature, they reported seven successful cases out of fifty two of various anastomotic procedures. When one realizes that almost all of these patients are within the first week of life, the significance of this achievement becomes greater. More recently Dennis² has reported the successful use of resection and primary anastomosis in nine cases of gangrenous or non reducible intussusceptions in children. The youngest child in this series was 39 days old the oldest being 9 years.

At the University of Minnesota Hospitals the use of single layer anastomosis over clamps as advocated by Winzenstein has been the procedure of choice. He has also advocated the use of aseptic decompression and primary anastomosis in selected cases of small bowel obstruction.³ The advantages of the 'long tube' intubation of Miller and Abbott as an adjuvant in intestinal obstruction are obvious. However the time lost in the placement of this tube in the small bowel precludes its use as the sole therapy in obstructions of a strangulating nature.

It is with this in mind that the following case of successful resection and primary end to end anastomosis of a strangulated gangrenous loop of bowel in a 19 day old infant is reported.

CASE REPORT

G. B. (U. M. No 79046) an 18 day old white male infant was admitted to the University of Minnesota Hospitals at 9 A. M. of June 10 1948. About 2 A. M. on the morning of June 10 1948, following the A. M. feeding the child began to grunt and cry as if in pain. The attacks were repeated every five to ten minutes and lasted for about two hours. Holding the child seemed to quiet him. For the next two feedings the infant took very little and whatever was taken was regurgitated. After that he remained somewhat quieter, crying only at infrequent intervals.

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK MD

PRIMARY TERATOMAS OF THE LATERAL RETROPERITONEAL SPACES

JOSEPH T. PALUMBO MD * KENNETH R. CROSS MD † ALFRED N. SMITH MD *
AND ALBERT A. BARONAS MD † DES MOINES IOWA

IN ADDITION to reporting a case of a primary teratoma of the left lateral retroperitoneal space successfully treated we will present a review and analysis of the literature available on this subject up to 1948. In the fifth seven cases reviewed the diagnosis was established by the pathologic examination of surgical or autopsy specimens. This review will include briefly the historical background, the histogenesis and the pathologic anatomy of this neoplasm. The overall incidence and the distribution of cases according to age and sex will be presented. The symptoms and signs, treatment and prognosis in these cases will be reviewed. This information may thus clarify the concept of an entity which is seldom discussed in medical reference volumes.

HISTORICAL

Pemberton and Whitlock¹⁸ credit Morgagni with the first description of a retroperitoneal tumor in 1761. Tumors in this location, unrelated by origin to adjacent organs, were shown to exist by Jobstein¹⁹ in 1829. The demonstration of a primary teratoma waited Dickinson's² case in 1871. This is the case that appears in association with the name Howship in several instances in the literature. This is mentioned to avoid confusion for the surgeon's name was W. Howship Dickinson.

HISTOGENESIS

We have no new theory relative to the origin of these tumors nor is it our intent to prove or disprove existing theories. The most popular concepts at present center about Spemann's²⁰ theory of embryonic primary organizers and their influence or lack of influence on the migration and growth of embryonic tissues. It is believed that the cells which escape organizer influence are related to the invagination, primitive streak since with few exceptions teratomas arise in an immediately preaxial median or paramedian location. Hansmann and Budd²¹ incriminated urocaudal rests as the site of origin. There is general agreement however as to their congenital nature and their origin from embryonic pluripotential cells. Their subsequent growth is not under the orderly

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and the Department of Pathology, Veterans Administration Hospital

In retrospect the most difficult part of the entire procedure was our inability to keep the child at a plane of anesthesia wherein straining and, thereby, eversion could be avoided.

Postoperative Course—The postoperative course was remarkably uneventful. The infant had a bowel movement on the first postoperative day and continued having three to five movements daily thereafter. Melen which was present at first soon disappeared. The child was discharged on normal feedings on the eleventh postoperative day.

Pathologic Report—"The gross specimen of the terminal ileum and cecum weighed 15 Gm. A loop of bowel measured 10 cm in length and 12 mm in diameter. There was an area of gangrene 4 cm in length. The line of resection came to within 1 cm of this area of gangrene at the nearest point. The terminal ileum and cecum were received in one piece. The terminal ileum measured 3 cm in length and 7 mm in diameter, the cecum 2.5 cm in length and 10 mm in diameter. The appendix measured 3.5 cm in length and 3 mm in diameter. No change was noted in this piece of the specimen.

Microscopic section of the loop of bowel which appeared grossly to be gangrenous showed extensive hemorrhage involving the serosa and muscularis. The mucosa appeared to be quite well preserved. The muscularis in some areas of the bowel was almost completely absent. The mesenteric vessels were congested with red blood cells. The appendix showed no change.

Conclusion—Strangulated bowel early gangrene.

Follow up—When last seen one month after surgery the child was normal in every respect. He had gained 5½ pounds.

SUMMARY

A case of primary resection of gangrenous ileum with anastomosis and survival in a 19 day old infant is presented. The cause of the strangulation was an inguinal hernia.

REFERENCES

1. Ladd, W. I. and Croft, P. F. *Abdominal Surgery of Infancy and Childhood*. Philadelphia 1941. W. B. Saunders Company.
2. Dennis, C. *Excision and Primary Anastomosis in the Treatment of Gangrenous or Non-gangrenous Bowel Obstruction*. 1947.
3. Wang, *Management of Bowel Obstruction*.
4. Dennis, *Gangrenous Bowel Surgery*. 22, 312. 1947.

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supervision of forces that maintain other tissues in a state of equilibrium. They are truly misdirected cells unleashed to their own devices and therefore dangerous. Needham¹⁷, Hamilton,¹⁸ and Willis²³ emphasized their belief that teratomas should no longer be considered as incomplete fetuses as has been commonly done.

ANATOMY AND PATHOLOGY

The retroperitoneal space is a potential space located between the posterior parietal peritoneal wall and the anterior aspect of the posterior body wall. Its cephalic limit is the diaphragm and its attachments to the body wall. The pelvic diaphragm forms its caudal limits. Laterally the boundaries correspond to the lateral borders of the ascending and descending colon and an imaginary projection of these lines in a sagittal plane. In defining the lateral retroperitoneal area, Witzel²¹ put the medial boundaries at the vertebral column and the inferior boundaries at the linea terminalis or the white line of the pelvis. This concept of the lateral retroperitoneal space is especially convenient from a clinical standpoint as serial teratomas are excluded.

The term 'primary' teratoma refers specifically to a teratoma arising independently and not from adjacent organs or structures. Metastatic tumors are also excluded by the term. A teratoma is characterized by Willis²³ as being a 'true tumor or neoplasm composed of multiple tissues of kinds foreign to the part in which it arises.' By the designation 'true' he eliminates parasitic fetuses and heterotopic accessory organoid tissue. This is based upon the observation that a parasitic fetus is a quiescent malformation. Accessory or heterotopic organoid tissue: a coordinated orderly growth coexistent with surrounding tissue—neoplastic qualities are missing. It is admitted that well differentiated teratomas do have mature adult tissue in some instances. This does not imply, however, that it is an orderly coexistent growth. We have found no record of a primary retroperitoneal teratoma being found incidentally at necropsy. It would not be surprising should one be found. In a fatal case reported by Hansmann and Budd²² the patient a man 51 years of age gave a history of a tender mass in the left upper abdominal quadrant at the age of 4 years. He succumbed to an infected teratoma in the left upper quadrant forty seven years later although the original mass had subsided forty six years previously. Therefore the true tumor characteristics of Willis²³ are borne out by our findings that after an unpredictable period of time retroperitoneal teratomas will become of clinical importance as a result of their growth. They are not subject to the regulating and restricting influences that the body exerts upon its normal tissues.

Embryomas and mixed tumors are differentiated by Willis²³ on the grounds that they represent tumors of tissues indigenous to an organ or region.

Simple dermoid cysts are differentiated on the basis of the lack of multiplicity of tissues. The findings of Pick and Wilms mentioned by Fung² on the high incidence of tissue multiplicity in the so called dermoid cysts when thoroughly examined should be kept in mind. For this reason we have been adverse to the use of the ubiquitous term 'dermoid cyst'.

We have made no attempt to classify the reported cases as to whether they were cystic or solid for practically all teratomas show a relative amount of both features unless obliterated by carcinomatous or sarcomatous changes

Of the fifty eight cases, the record of which we have compiled in Table I, in which there were reasonably acceptable pathologic examinations there were six cases in which malignant degeneration was present, or an incidence of 10 per cent In Meccay's case,¹⁸ the patient developed local recurrence and metastasis despite the fact that no evidence of malignancy was found in the teratoma at the time of removal Watanabe's patient²¹ showed carcinomatous metastasis at the age of 23 months Follow up studies on most cases were poor and it may be assumed that the incidence of malignancy is higher than we have stated Also the microscopic data on many cases were hard to evaluate Teratomas differ in their malignant tendencies depending upon their location, as pointed out by Fwing.² Our statistics should not be compared to those dealing with teratomas of other sites

The largest teratoma reported in this region weighed twenty six pounds and was successfully removed by Cordon.¹⁹

In general these neoplasms occurred in a ratio of 2:1 in the left side Accurate determination of the point of origin was not always possible

INCIDENCE

Evaluation of the incidence of this neoplasm was difficult because no large series has been reported from a single source In 301 cases of malignant tumors in children Farber⁶ reported one case of retroperitoneal teratoid tumor Donnelly² reported two teratomas in 95 consecutive primary retroperitoneal tumors in all ages This series covered a twenty year period and represented an approximate incidence of one case per 170 000 hospital admissions⁴ Donnelly² further estimated that there were 500 primary retroperitoneal tumors reported up to 1946 Of our collected cases 55 correspond to that time limit which indicates that 11 per cent of primary retroperitoneal tumors are teratomas In the series of retroperitoneal tumors reported by Frank 93 per cent were teratomas Gobbil⁸ collected 80 retroperitoneal tumors 5 of which fulfilled the requirements of primary retroperitoneal teratomas

We consider 58 cases which includes our own as bona fide primary retroperitoneal teratomas We were unable to verify pathologically the two cases of Ima and Baljassay reported by Meccay and Frazier¹⁸ The case reported by Fuller and Jagger³ did not meet the requirements in that the neoplasm did not originate in the lateral retroperitoneal space Judd and Fulcher² gave no pathologic reports on their two cases For these reasons these five cases were dropped from consideration

AGE

The average age of the reported cases at the time of the diagnosis was 13 years Fifty five per cent of these were in the first decade and 30 per cent were diagnosed during the first year of life Ten per cent occurred in the second decade while a secondary peak was noted in the third decade with an incidence of 25 per cent Only 10 per cent occurred after the age of thirty The oldest individual reported by Gobbil⁸ was 53 years of age

TABLE I CASES OF RETROPERITONEAL TERATOMA REPORTED IN LITERATURE

AUTHOR	SEX	AGE	LOCATION	OPERATED	RESULT	SYMPTOMS
Arnheim ¹	F	mo	left	Yes	Lived	Abdominal enlargement WBC 16 000 constipation
Mayer A Beitr z klin Chir 75 2-6 1911	M	14 yr	left	Yes	Died	Abdominal mass pain weight loss dilated veins
Brouha A Rev de gynec e d ob t 6 401 1902	F	6 yr	left	Yes	Died	F
Budde W Beitr z path Anat 75 307 19-6 quoted by Arnheim ¹	M	mo	Left and right	Yes	Died	Abdominal mass dilated veins vomiting
Hardenbeurer B quoted by Gobell ⁹	F	17 yr	right	Yes	Died	Abdominal mass
Campbell M J J Urol 29 677, 19 3	M	6 mo	L.L.Q.	Yes	Lived	Abdominal mass constipation weight loss
Dickinson ²	F	yr	L.L.Q.	No	Died	Abdominal mass
Donnelly ³	F	F	F	Yes	F	F
Durante G and Davil C Bull et m m Soc anat de Paris 82 328, 1907 quoted by Arnheim ¹	F	Neo natal	Left and right	No	Died	F
Gerland L D Nederl tijdschr v verlosk en gynaec 41 56, 1938 quoted by Arnheim ¹	F	8 mo	Left and right	Yes	Lived	Abdominal mass
Proboere C Frankfurt Ztschr f Path 43 222 193 quoted by Arnheim ¹	F	10 mo	R.U.Q.	No	Died	Abdominal enlargement
Feldmann, I Centralbl f allg Path u path Anat 48 3-1 1930	M	0 yr	L.U.Q.	No	Died	Abdominal mass
Cale C and Willis R J Path & Bact 56 40 1944	F	13 yr	Left and right	Yes	Lived	Abdominal mass
Gobell ⁹	F	23 yr	Left	Yes	Died metastases	Abdominal mass pain
(Gordon ¹¹)	F	20 yr	Right	Yes	Lived	Abdominal mass
Gros A As franc de chir Proc verb 7 666 1893 quoted by Meernay and Frazier ¹⁶	F	26 yr	R.U.Q.	Yes	Lived	Abdominal mass
Gule H W W Greifs wall 1898 F W Kunike quoted by Gobell ⁹	M	9 yr	L.L.Q.	Yes	Died	Abdominal mass
Hansmann and Buidis ¹²	M	31 yr	L.U.Q.	Yes	Died	Lumbar pain fever
Homer H Boston M & S J 102 C1 1880	F	8 mo	Right	No	Died	Abdominal mass fever weight loss
Johnson R and Lawrence T Proc Pav Soc Med 3 43 1909	M	3 yr	Left	Yes	Died	Abdominal mass
Kineko Y Ginn 18 17 19-1 quoted by Meernay ¹⁶	M	10 mo	Left and right	No	Died	Abdominal mass

Malignant.

TABLE I—CONT'D

AUTHOR	SEX	AGE	LOCATION	OPERATED	RESULT	SYMPTOMS
Kolb H. quoted by Fortu- gal	F	7 wk	Left	No	Died	Abdominal mass dilated veins
Kon J. Tokio M. Soc 16 1904 quoted by Terasako	M	4 yr	Left	Yes	Died	Abdominal mass
Koitch M. Compt rend Soc de biol 90 1081, 1924	M	4 yr	L.U.Q.	Yes	Died	Abdominal mass pain
Kuznetsov, D. D. Med pribov k mor k sborniku, p 101 1910	M	4 mo	Left	Yes	Died	Abdominal mass, constipation
Landivar, A. F., and Ipar- raguirre C. A. Bol. y trab Soc de cir de Buenos Aires 19 837, 1930 quoted by Meerav ¹⁶	M	4 yr	L.U.Q.	Yes	Lived	Abdominal
Lexer E. Arch f klin Chr 61 648 1900	F	11 yr	L.U.Q.	Yes	Lived	Abdominal mass pain fever
Lichtwood, H. Proc Roy Soc Med 25 17-6, 1930	F	7 wk	R.U.Q.	Yes	Lived	Abdominal en- largement mass constipation
Lundblad O. Acta chir Scandinav 72 174 1932	F	4 yr	f	Yes	Died	f
Lundblad O. ibid	F	4 yr	f	Yes	Lived	f
Lundblad O. ibid	F	5 yr	f	Yes	Died	f
Marchand F. Breslau aerztl Ztschr 3 251 1881 quoted by Portugal	F	5 yr	L.U.Q.	Yes	Died	f
Maydl ¹⁸	F	f	f	Yes	f	f
Meerav and Frazier ¹⁶	M	7 yr	R.U.Q.	Yes	Occurred metas- tases	Abdominal pain, WBC 15,000
Meckel J. F. Handb d path anatomie Leipzig Reclam 1812 quoted by Portugal	f	f	L.U.Q.	No	Died	f
Nicholson C. M. Am J Clin M 13 343 1906	M	1 yr	R.U.Q.	Yes	Died	Abdominal mass pain vomiting
Nicholson C. W. I. Guye Hosp Rep 85 3, 9 1930	F	7 mo	Right	Yes	Lived	Abdominal mass pain
Nicholson C. W. I. J Path & Bact 32 70, 1929	F	4 mo	L.U.Q.	No	Died	f
O'Leary C. M. and Hal- pert B. SURGERY 21 194 194	F	10 mo	R.L.Q.	Yes	Lived	Abdominal en- largement and mass
Paulauf R. Centralbl f allg Path. 53 130 1931	F	5 mo	Left	No	Died	Abdominal mass
Pillet A. Bull Soc anat de Par 63 870 1888 quoted by Meerav ¹⁶	F	4 yr	Left and right	Yes	Died sarcoma	Abdominal mass
Portugal J. F. Thèse de Bordeaux No 11 1919	F	1 yr	L.U.Q.	Yes	Died	Abdominal mass pain, vomiting
Roux J. J. Compt rend Soc de biol 3 291, 1836 quoted by Meerav ¹⁶	F	5 yr	Left and right	No	Died	Abdominal mass uremia
Ruge ¹⁹	M	yr	Left	Yes	f	f

(Continued on following page)

TABLE I—CONT'D

AUTHOR	SEX	AGE	LOCATION	OPERATED	RESULT	SYMPTOMS
Sand H and Lerat I Bull Acad. de méd Belge 26 115 1912 quoted by Arnheim ¹	M	13 yr	Left	Yes	Died	Abdominal mass fever
Schonholzer G Beitr z path Anat u z allg Path 40 349 1906	M	- yr	L U Q	No	Died	Abdominal mass
Seki M Gann 21 10 1927, quoted by Meecray ¹⁶	M	- mo	Left	No	Died	Abdominal mass
Smith E and Cochrane W Canad M A J 55 151 1946	M	2 mo	L U Q	Yes	Lived	Abdominal enlargement and mass
Terasako S Okayama Igakkai Zasshi 46 435, 1934	M	3 mo	Right	No	Died	Abdominal mass
Tilloux M Gaz d hop 59 757 1886 quoted by Meecray ¹⁶	F	- yr	L U Q	Yes	Died	Abdominal mass
Frethowan W and Dale J M J Australia 1 540 1924	F	24 yr	R L Q	Yes	Lived	Abdominal enlargement and mass
Tsuji I Japanese Surg A 21 1920 quoted by Terasako	M	17 mo	Left	Yes	Died	Abdominal mass
Usandizago M and Mayor J Arch de méd cir y especialid 34 596	F	-8 yr	L L Q	Yes	Lived	Abdominal pain
						Abdominal mass
						Abdominal mass
Willis ²	F	9 mo	R L Q	†	Died	†
Willis ²²	F	9 wk	R U Q	Yes	Lived	Abdominal mass
Our case	M	44 yr	L U Q	Yes	Lived	Backache

SEX

The sex was not recorded in four cases. Of the remainder 57 per cent were females and 43 per cent were males.

SYMPTOMS AND FINDINGS

Abdominal enlargement and a palpable mass are the most common findings in these cases. The symptoms are vague and not alarming until the growth of the tumor is well advanced. They are predominantly the result of pressure incident to the growth of the neoplasm. They frequently include abdominal or back pain. There are symptoms of intestinal obstruction with nausea, vomiting, constipation and weight loss in some cases. Less frequently the symptoms are referable to the urinary system. It is not uncommon to find dilatation and prominence of the veins of the anterior abdominal wall as collateral circulation is established. Secondary edema of the lower extremities may result. The tumor may transmit aortic pulsations. Its motility is generally limited. Occasionally, a low grade fever has been recorded in children but Meecray and Frazier¹⁶ stated that fever is more common in retroperitoneal sarcomas.

DIAGNOSIS

The specific diagnosis is usually not possible preoperatively particularly when calcific deposits cannot be seen in roentgenograms. Given a case with an abdominal mass regardless of symptomatology unless acute, time should be taken to localize the site by means of roentgen studies of the gastrointestinal and urinary tracts. This will also give the surgeon some evaluation of the integrity and function of adjacent organs and structures and it may determine the operability of the tumor and/or the type of surgery to be performed.

Donnelly³ investigating primary retroperitoneal tumors of all types stated that they are most frequent in men in a ratio of approximately 2:1 and that they occurred chiefly in the fourth and fifth decades of life. This we feel is of diagnostic significance for in the case of teratomas only 5.5 per cent of the cases occur in that age group and they are slightly more common in women.

PROGNOSIS

The overall mortality in this group was 70 per cent. Four cases (Donnelly³, Maydl¹⁵, Ruess¹⁹ and Willis²²) are excluded here because of insufficient data. Of the 39 cases with operation in which the outcome was stated the patient mortality was 34 per cent. An analysis of the cases with operation during the past ten years which number 6 including our own reveals that the patient mortality has been 0.

Judging from this series, 10 per cent of the teratomas may be expected to be malignant at the time of the operation. Early removal of the teratomas will be accompanied by a reduction in the number showing malignancy.

CASE REPORT

(J. a 43-year-old white man, a truck driver, was admitted to the hospital May 11, 1948, complaining of a low backache of five week duration. This began after lifting the side of a truck box which weighed approximately 60 pounds. After an x-ray examination by the referring physician he was treated with hot baths. A lumbo-sacral belt was applied which gave no relief. The pain was constant and dull. It was aggravated by prolonged standing, lifting, bending, and jolting. There was periodic radiation into the right hip with extension down the lateral aspect of the thigh. There had been no numbness or paresthesia.

The patient had had a fracture of the pelvis in 1937 when he was thrown by a cyclone. Since that time he had had periodic right hip pain. For the pain he was admitted to this hospital in 1944 and 1945. On both occasions the x-ray examination revealed slight deformity of the right pubic and ischial rami. This was interpreted as residuals of the previous fracture. The remaining past medical history was irrelevant.

Physical examination was complete. Hyperextension of the lumbar spine aggravated the pain in that area. No other abnormalities were found. Clinical laboratory examination, including a complete blood count and hemoglobin determination, Kahn test, urinalysis, blood sugar, total plasma protein, and nonprotein nitrogen determination, were all within the limits of normal.

A postero-anterior roentgenogram of the chest was within normal limits. A routine roentgenogram (anteroposterior and lateral) of the lumbar spine revealed no significant bony disease or injury except for an old healed fracture of the right hemipelvis. However in the anteroposterior projection (Fig. 1) an oval shadow of egg-bell configuration was seen in the apex of the L1 pars interarticularis medial to the left kidney. At its superior pole a small dense opaque shadow was visible which suggested a small fragment of tooth. Near the inferior

pole an irregular calcific plaque was visible which appeared to be essentially an amorphous calcium deposit. The renal shadow was displaced somewhat cephalad and laterally. In the upright position no fluid levels were seen nor was the interior of the shadow reticulated or suggestive of "matted hair."

Intravenous and retrograde pyelograms were entirely within normal limits, except for slight dilatation of the left renal pelvis and displacement of the renal shadow, demonstrated in the conventional and oblique views (Figs. 2 and 3). The evidence supported the view that the lesion was retroperitoneal and undoubtedly a teratoma.

Operative Findings.—On June 7, 1949, under nitrous oxide anesthesia, the left posterior retroperitoneal space from the diaphragm to the sacral promontory was exposed through a left oblique lumbar incision utilizing the retroperitoneal approach.



Fig. 1

Fig. 1—Roentgenogram (anteroposterior) showing an oval shadow of crescentic configuration in apex of the lungs shadow, indicating the left kidney.



Fig. 2

Fig. 2—Retrograde pyelogram (anteroposterior) showing lateral displacement of left kidney.

A thick-walled, smooth, fluctuant mass was found attached to the left lateral aspect of the body and transverse processes of the first to the fourth lumbar vertebrae. The sacculated 13 cm. in length and 6 cm. in diameter. It was buried in the fibers of the left psoas muscle and was attached by thick fibrous strands to this structure and to the adjoining vertebrae. The most densely adherent point was at the superior pole. It contained in addition to fluid a ball of hair. There were two areas of calcification in the wall. After aspiration of 100 cc. of greenish-yellow turbid material the mass was reduced in size to facilitate its complete dissection and removal. Careful dissection was necessary to free the left genitofemoral and femoral cutaneous nerve. Bleeding was controlled by Gelfoam and Orsiel. Two Penrose drains were placed through a stab wound in the loin. The wound was closed in layers.

Surgical Pathologic Findings.—The inner surface of the cyst wall was smooth for the most part but was rough and hemorrhagic in a few areas. It was trabeculated. At many points there were large pores filled with cheesy material. Two small masses of hair and sebaceous material and the two calcified masses previously described were found in the wall.



Fig 3—Retrograde pyelogram (oblique) showing anterior displacement of left kidney

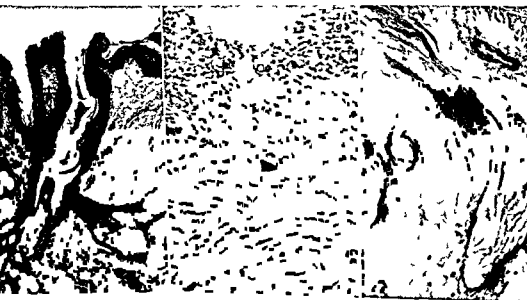


Fig 4

Fig 5

Fig 6

Fig 4—Hematoxylin and eosin stain (X50). Cyst wall showing squamous epithelium, hair follicle and sebaceous gland.

Fig 5—Hematoxylin and eosin stain (X100). Cyst wall consisting of granulation tissue.

Fig 6—Hematoxylin and eosin stain (X100). Decalcified compact bone from cyst wall.

Microscopically the lining consisted of a thin layer of squamous epithelium (Fig 4). In the subcutaneous tissue numerous large sebaceous glands were seen. Hair follicles were present. Areas which appeared roughened and hemorrhagic were lined by granulation tissue (Fig 5). A dense fibrous connective tissue stroma was infiltrated with lymphocytes, plasma cells and many large mononuclear cells. A few giant cells were seen. Both small and diffuse areas of recent hemorrhage were numerous. Peripherally, the wall was made up of scarred fat and striated muscle showing some round-cell infiltration, particularly in perivascular locations. Two large myelinated nerve trunks of normal structure were seen. Decalcified tissue revealed small areas of bone closely incorporated in the fibrous wall of the cyst (Fig 6). Intramembranous bone formation was apparent. Some calcium salts were deposited in the fibrous tissue. No evidence of entodermal structure was found. No evidence of malignancy was apparent.



Fig 7.—Retrograde pyelogram (anteroposterior) postoperatively showing the left kidney in a less lateral position.

Course in Hospital.—Postoperatively the drains were removed on the third day; the patient was ambulatory on the fourth day and the wound healed by primary intention. On the second day there was hypesthesia along the distribution of the left genitofemoral nerve and loss of the left cremasteric reflex. On the eighth day an erythematous pruritic rash appeared along the distribution of the left medial femoral cutaneous nerve. This subsided by the fourteenth day. An intravenous pyelogram on the fifteenth day revealed that the left kidney had returned some distance toward the midline. The patient was discharged on the twenty-fifth postoperative day with functional impairment of the left genitofemoral nerve.

Postdischarge Note.—The patient was readmitted for the follow-up examination on Oct 6, 1948, three months after discharge. He stated that the periodic discomfort in the right hip was still present. A burning pain aggravated by heavy lifting was present in the periumbilical area. The patient had been otherwise asymptomatic. There was an umbilical hernia present which measured approximately 1 cm in diameter. The neurological examination including the lower extremities was negative. X-ray studies of the lumbar and dorsal spine and the retrograde pyelogram (Fig 7) revealed no abnormalities. An umbilical hernioplasty was performed on Oct 13, 1948, with an uneventful postoperative convalescence. Again examination of the testicles revealed no abnormalities.

SUMMARY

A review of fifty seven primary teratomas of the lateral retroperitoneal spaces is presented. An additional case has been studied and the patient successfully treated by us. The origin of these tumors can only be theorized. In this series 10 per cent of the teratomas had undergone malignant changes. The remaining teratomas caused symptoms of pressure as their local growth encroached on surrounding organs. Commensurate with its congenital nature the tumor manifests itself most frequently in persons of the younger age groups. A slightly higher incidence of occurrence has been found in females than in males. The left side was twice as frequently the site of origin as was the right side. The size of the growth is variable and of no benefit in differentiating teratomas from other tumors of the retroperitoneal spaces. Diagnosis can be expedited by roentgenologic evidence of bones or teeth within the tumor. When such positive objective evidence is lacking the diagnostician is beset with the difficult problem of giving a preoperative diagnosis. By virtue of an understanding of the clinical characteristics of the individual tumor types this problem can be met. We have attempted to find clinical characteristics of diagnostic significance in these compiled cases of retroperitoneal teratomas.

The authors wish to express their appreciation to Dr. C. A. Voelker, Chief of the Department of Radiology for his interpretation of the roentgenograms.

REFERENCES

1. Arnhem E. D. 101, J. Mt. Sinai H.
2. Dickinson W.
3. Donnelly B. 70, 1946
4. Donnelly B.
5. Ewing J. 19 p. 1041
6. Farber G. Arnhem
7. Frank R. T.
8. Fuller C. B. 32, 176
9. Cobell I. Zur Kenntnis der Lateral Retroperitoneal Tumoren. Deutsche Zeitschrift f. Chirurg. 61, 1, 1901.
10. Gordon O. A. Teratomata—Ovarian and Retroperitoneal, Surg. Gynec. & Obst. 41, 299, 1925.
11. Hamilton W. J., Boyd J. D. and Mossman H. W. Human Embryology. Baltimore 1945. Williams & Wilkins Company, p. 29.
12. Hansmann G. H. and Bull J. W. Massive Unattached Retroperitoneal Tumor. Am. J. Path. 7, 31, 1931.
13. Jull E. G. and Fulcher O. Dermoid Cysts of Abdomen. S. Clin. North America 13, 335, 1931.
14. Lohstein J. F. Lehrbuch der pathologischen Anatomie. Vol. I. II. Deutsche Bearbeitung von A. Neuhoff. Stuttgart 1874-1875. F. Brodhag quoted by Cobell.
15. Maydl K. Wien klin. Wochenschau 10, 293, 1896, quoted by Meccray and Frazier.
16. Meccray I. M. and Frazier W. D. Retroperitoneal Teratoma. Arch. Surg. 35, 358, 1917.
17. Needham J. Order and Life. London 1936. Cambridge University Press.
18. Pemberton J. De J. and Whitlock M. E. Large Retroperitoneal Lipoma. S. Clin. North America 13, 335, 1931.
19. Dermoid Cyst. Beim Manne. Frazier.
20. Haven 1938. Yale University.
21. Witzel O. Beiträge zur Chirurgie der Bauchorgane. Deutsche Zeitschrift f. Chirurg. 24, 301, 1901. quoted by Cobell.
22. Willk. R. A.
23. Willk. R. A.
24. Watanabe M. Teratom 40, 1, 1935. C. A. Moore Company, p. 940. Teilweise Krebsig Entartetem abstrah. Am. J. Cancer 20.

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SURGERY

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ACUTE PANCREATITIS PATHWAYS OF ENZYMES INTO THE BLOOD STREAM

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ONE of the problems of the pathologic physiology of acute pancreatitis is to explain the rise in serum enzymes which accompanies it and to determine whether this elevation has itself any significant clinical effects.

In man the pancreas and the major salivary glands are known to contain and to secrete into the gastrointestinal tract large amounts of the enzyme amylase. Injury to one of these organs particularly the pancreas in the form of acute external trauma or acute inflammation is associated with a rise in the concentration of amylase in the blood stream.

Indirect evidence is already at hand pointing to the damaged pancreas as the source of the additional amylase and absorption into the pancreatic venous blood as the most important route of dissemination. Popper and Necheles¹ cannulated the thoracic duct of the dog and collected the lymph for amylase determination. They then traumatized the pancreas. With the lymph exteriorized the blood concentration rapidly increased. Furthermore, the lymph amylase collected was small in total amount although concentrated. They also found that ligation of the portal vein delayed or prevented the rise in concentration of the amylase in the peripheral blood. That the rise of amylase in the serum is due chiefly to lymphatic absorption is therefore unlikely. The rise in concentration of serum amylase must then be due chiefly to the absorption of the enzyme directly into the blood stream from the damaged pancreas or it must be absorbed indirectly after excretion into the intestinal tract. Introduction of large amounts of amylase into the gastrointestinal tract has not been associated with any rise in serum amylase.²

This study has been undertaken to show directly whether or not the injured pancreas is the source of the additional serum amylase and if so by what route the additional enzyme reaches the serum.

EXPERIMENTAL

Ten healthy dogs were used as the experimental animals. The dog was chosen because his salivary glands do not secrete amylase² and therefore one variable was eliminated. The experiment was designed to produce two somewhat comparable episodes of acute pancreatitis in each dog within a space of

ANNOUNCEMENT

BRITISH AMERICAN EXCHANGE FELLOWSHIPS IN CANCER RESEARCH

AWARDED UPON RECOMMENDATION OF THE COMMITTEE ON GROWTH OF THE
NATIONAL RESEARCH COUNCIL

British American Exchange Fellowships in Cancer Research of the American Cancer Society, awarded by the Society upon recommendation of the Committee on Growth of the National Research Council are offered to citizens of the United States for advanced training and experience in Great Britain in specialized fields of investigation pertaining to the problem of cancer. Similar fellowships are awarded by the British Empire Cancer Campaign to British scientists for study in the United States. The Society and the Committee on Growth welcome the cooperation of universities and hospitals in making known these opportunities to suitable candidates.

FIELDS OF STUDY

These fellowships are awarded by the American Cancer Society to provide specialized training for American investigators in Great Britain where opportunities exist for fully in fields of research in malignant disease not widely available in this country. Training for an equal number of young British scientists selected by the Campaign will be provided in this country. The Society, the Committee on Growth and the British Empire Cancer Campaign believe that the training of young men and women in the many complex disciplines of modern scientific thought and techniques are fundamental to a sound approach to the problem of human cancer.

neoplastic growth in specialized scientific areas in which superior facilities exist in Great Britain.

QUALIFICATIONS OF APPLICANTS

Fellowships are open to citizens of the United States who possess the degree of Doctor of Medicine, Doctor of Philosophy or Doctor of Science. They are intended for young men and women embarking upon a career in clinical medicine or basic research in the cancer field.

Applications should show the field of research in Great Britain, the individual under whom the fellow desires to work, what problem he intends to investigate, when he wishes to start.

CONDITIONS OF APPOINTMENT

Fellowships will be awarded for a period of one year.

The annual stipend will be £1000 (\$4020.00). An allowance of \$600.00 is made for travel to the site of the fellowship in Great Britain.

University staff appointment with teaching duties agreeable to the fellow is permitted provided it carries no additional salary and provided it is acceptable to the Committee on Growth, the American Cancer Society, and the British Empire Cancer Campaign. No other remunerative work will be permitted during the tenure of the fellowship.

Fellowship appointments are subject to the condition that once accepted they will not be vacated or the place of work changed within the period of tenure without the consent of the Committee on Growth, the American Cancer Society, and the British Empire Cancer Campaign.

TIME OF APPLICATION

Applications may be made to the Committee on Growth, the American Cancer Society, or the British Empire Cancer Campaign. The Committee on Growth will forward applications to the American Cancer Society and is subject to all conditions of the Society. Fellowships will be made effective at the convenience of the institution and the fellow.

ATLAS CONCENTRATION

		CONTROL STUDIES BEFORE AND AFTER ANESTHESIA		20 cc Bile Injected into Pancreatic Duct—Production of Pancreatitis, 2nd exper							
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-	904	-	488	-	-	588	-	638	-	-	81
-	890	490	490	-	-	-	-	641	-	-	-
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1111	4088	-	416	503	568	681	88	1190	193	-	-
801	893	-	420	443	467	499	538	606	761	-	80
-	-	414	416	-	-	489	-	611	-	-	79
-	-	413	413	-	-	-	-	615	-	-	-
-	Conc	Neg	-	-	-	-	-	Pre ent	-	-	Pre c
604	2888	-	552	690	743	803	97	1343	188	-	-
799	83	-	556	588	631	669	693	744	790	-	84
-	-	563	560	-	-	664	-	755	-	-	83
-	-	559	566	-	-	-	-	-	-	-	-
-	Present	Neg	-	-	-	-	-	Neg	-	-	Pre c
514	467	-	443	453	618	914	1318	1803	310	-	461
-	-	-	-	461	483	492	544	826	89	-	91
619	863	45	450	-	-	501	-	830	-	-	94
-	-	449	414	-	-	-	-	844	-	-	-
-	Conc	Neg	-	-	-	-	-	Pre ent	-	-	Cor
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803	1211	-	552	-	-	-	-	-	-	-	-
-	1219	-	554	584	617	647	736	818	948	-	136
-	-	558	553	-	-	64	-	826	-	-	134
-	Conc	Neg	-	-	-	-	-	813	-	-	135
167	138	-	500	-	-	-	-	Conc	-	-	Con
103	859	-	513	511	634	71	839	14	1193	-	168
-	864	-	509	536	581	598	612	770	-	-	93
-	811	503	506	-	-	603	-	784	816	-	9
-	-	499	-	-	-	-	-	890	-	-	97
-	Trace	Neg	-	-	-	-	-	881	-	-	-
108	14	-	480	541	621	723	909	118	1431	-	105
87	1001	-	511	515	530	566	581	664	78	-	108
-	1011	515	518	-	-	560	-	660	-	-	109
-	998	516	512	-	-	-	-	649	-	-	-
-	Conc	Neg	-	-	-	-	-	Neg	-	-	Con
84	13	-	511	768	813	881	96	1013	1148	-	130
631	64	-	515	693	704	72	781	809	8	-	8
23	91	-	518	73	748	793	875	934	1018	-	109
-	71	580	686	-	-	-	-	815	-	-	85
-	-	581	686	-	-	-	-	801	-	-	-
-	Neg	Neg	-	-	-	-	-	Neg	-	-	Pre c
123	115	-	475	503	629	798	913	1416	19	-	114
698	105	-	455	469	511	543	588	-	912	-	131
85	157	488	455	473	549	581	740	91	1405	-	133
-	1017	455	461	-	-	540	-	731	-	-	13
-	Con	Neg	-	-	-	-	-	Neg	-	-	Con
1410	1808	-	504	613	794	1035	1261	1734	203	-	251
930	1115	-	518	561	608	706	793	959	-	-	16
1015	139	514	514	566	701	88	934	948	123	-	161
-	1101	518	518	-	-	716	-	17	170	-	211
-	-	Neg	50	-	-	-	-	960	-	-	160
-	Present	-	-	-	-	-	-	950	-	-	Con

TABLE I SERUM

CONTROL STUDIES BEFORE AND AFTER ANESTHESIA									
MINUTES AFTER PANCREATIC TRAUMA									
					5	10	15	20	30
Pancreatic vein	-	481	480		518	60	831	1116	160
Pancreatic artery	-	502	-		-	-	-	-	-
Aorta	-	500	501		413	524	561	502	679
Femoral vein	501	504	-		-	-	-	-	64
Femoral artery	506	501	-		-	-	-	-	644
Urine	Neg	-	-		-	-	-	-	Present
Pancreatic vein	-	512	580		488	611	1143	1811	2861
Pancreatic artery	-	323	-		-	-	-	-	73
Aorta	-	390	389		390	437	501	614	119
Femoral vein	400	399	-		-	-	-	-	128
Femoral artery	394	395	-		-	-	-	-	71
Urine	Neg	-	-		-	-	-	-	Present
Pancreatic vein	-	566	561		784	-	1111	1660	191
Pancreatic artery	-	580	-		-	-	-	-	-
Aorta	-	580	589		617	632	651	651	711
Femoral vein	559	581	-		-	-	-	-	180
Femoral artery	516	581	-		-	-	-	-	-
Urine	Neg	-	-		-	-	-	-	Neg
Pancreatic vein	-	371	415		411	464	-	1111	168
Pancreatic artery	-	414	-		-	-	-	510	-
Aorta	-	416	412		429	466	-	503	574
Femoral vein	416	408	-		-	-	-	-	51
Femoral artery	42	419	-		-	-	-	-	531
Urine	Neg	-	-		-	-	-	-	Present
Pancreatic vein	-	531	538		660	811	913	983	1115
Pancreatic artery	-	543	-		-	-	-	-	-
Aorta	-	546	544		570	600	611	630	651
Femoral vein	550	546	-		-	-	-	-	640
Femoral artery	548	542	-		-	-	-	-	644
Urine	Neg	-	-		-	-	-	-	Present
Pancreatic vein	-	411	471		511	610	651	801	1141
Pancreatic artery	-	414	-		-	-	-	510	691
Aorta	-	476	475		490	508	541	571	68
Femoral vein	481	477	-		-	-	-	-	610
Femoral artery	480	480	-		-	-	-	-	618
Urine	Neg	-	-		-	-	-	-	Neg
Pancreatic vein	-	411	411		530	641	811	914	1115
Pancreatic artery	-	431	-		-	-	-	-	-
Aorta	-	431	438		451	488	498	518	601
Femoral vein	410	418	-		-	-	-	-	614
Femoral artery	418	431	-		-	-	-	-	610
Urine	Neg	-	-		-	-	-	-	Neg
Pancreatic vein	-	619	615		618	614	618	611	611
Pancreatic artery	-	63	-		-	-	-	-	618
Aorta	-	63	631		634	63	633	641	611
Portal	-	631	61		626	61	634	610	610
Femoral vein	635	636	-		-	-	-	-	611
Femoral artery	631	636	-		-	-	-	-	611
Urine	Neg	-	-		-	-	-	-	Neg
Pancreatic vein	-	411	430		448	471	583	610	615
Pancreatic artery	-	461	-		-	-	-	-	-
Aorta	-	458	454		451	467	461	571	611
Femoral vein	-	458	458		-	-	-	-	709
Femoral artery	460	459	-		-	-	-	-	611
Femoral artery	463	451	-		-	-	-	-	610
Urine	Neg	-	-		-	-	-	-	Neg
Pancreatic vein	-	513	510		606	613	811	911	1163
Pancreatic artery	-	513	-		-	-	-	-	-
Aorta	-	578	518		581	614	619	711	804
Femoral vein	-	598	519		-	-	-	-	913
Femoral artery	-	575	-		-	-	-	-	811
Femoral vein	571	575	-		-	-	-	-	801
Femoral artery	573	575	-		-	-	-	-	801
Urine	Neg	-	-		-	-	-	-	Neg

Ligation of thoracic duct was completed at completion of this phase of the experiment in all

		CONTROL STUDIES BEFORE AND AFTER ANESTHESIA				2.0 cc Bile Injected into Intracerebral Duct—Production of Incretin, 2nd Experiment									
40	60					5	10	15	20	30	40	50	60	70	80
-	311	-	-	481	-	515	592	750	918	1224	-	-	-	-	-
-	895	-	-	-	-	499	531	581	600	615	-	-	-	-	8
-	904	-	-	498	-	-	-	588	-	638	-	-	-	-	8
-	890	-	-	488	-	-	-	-	-	641	-	-	-	-	-
-	Conc	-	-	Neg	-	-	-	-	-	Neg	-	-	-	-	1 re
311	4088	-	-	416	-	503	568	681	882	1140	1832	-	-	-	-
801	803	-	-	420	-	443	467	499	538	606	701	-	-	-	8
-	-	-	-	416	-	-	-	489	-	611	-	-	-	-	-
-	-	-	-	413	-	-	-	-	-	615	-	-	-	-	-
-	Conc	-	-	-	-	-	-	-	-	Pre ent	-	-	-	-	1 re
404	488	-	-	552	-	690	743	803	977	1343	1882	-	-	-	-
709	837	-	-	556	-	588	641	669	693	744	790	-	-	-	8
-	-	-	-	560	-	-	-	664	-	752	-	-	-	-	8
-	-	-	-	566	-	-	-	-	-	-	-	-	-	-	-
-	Present	-	-	Neg	-	-	-	-	-	Neg	-	-	-	-	1 re
314	464	-	-	443	-	453	678	914	1318	1804	3720	-	-	-	46
619	863	-	-	449	-	461	483	492	544	826	892	-	-	-	9
-	-	-	-	450	-	-	-	501	-	830	-	-	-	-	9
-	-	-	-	414	-	-	-	-	-	844	-	-	-	-	-
-	Conc	-	-	-	-	-	-	-	-	Pre ent	-	-	-	-	Con
1966	3076	-	-	552	-	603	718	962	1242	1509	224	-	-	-	-
803	1211	-	-	554	-	584	617	647	736	818	948	-	-	-	130
-	-	-	-	553	-	-	-	642	-	826	-	-	-	-	130
-	-	-	-	500	-	-	-	-	-	813	-	-	-	-	130
-	Conc	-	-	Neg	-	-	-	-	-	Conc	-	-	-	-	Con
1612	1338	-	-	513	-	514	634	712	831	1422	1713	-	-	-	268
703	864	-	-	509	-	536	581	598	612	770	-	-	-	-	92
-	841	-	-	506	-	-	-	603	-	790	816	-	-	-	92
-	-	-	-	414	-	-	-	-	-	781	-	-	-	-	97
-	Trace	-	-	Neg	-	-	-	-	-	-	-	-	-	-	-
1082	14	-	-	480	-	591	621	723	903	1182	1433	-	-	-	22
8	1001	-	-	513	-	515	530	566	581	664	782	-	-	-	108
-	1011	-	-	518	-	-	-	560	-	660	-	-	-	-	109
-	918	-	-	512	-	-	-	-	-	649	-	-	-	-	-
-	Con	-	-	Neg	-	-	-	-	-	Neg	-	-	-	-	Con
84	133	-	-	612	-	68	813	881	912	1013	1148	-	-	-	130
691	64	-	-	686	-	693	704	727	781	809	822	-	-	-	92
723	1	-	-	680	-	732	748	793	875	934	1048	-	-	-	92
-	-	-	-	681	-	-	-	-	-	915	-	-	-	-	109
-	-	-	-	675	-	-	-	-	-	801	-	-	-	-	5
-	Neg	-	-	Neg	-	-	-	-	-	Neg	-	-	-	-	1 re
1203	132	-	-	415	-	503	629	74	933	1416	1722	-	-	-	230
698	1032	-	-	425	-	469	511	543	588	626	912	-	-	-	1310
18	1017	-	-	461	-	473	549	581	740	902	1405	-	-	-	1270
-	-	-	-	459	-	-	-	540	-	731	-	-	-	-	1800
-	Con	-	-	Neg	-	-	-	-	-	731	-	-	-	-	1300
1440	1608	-	-	504	-	613	794	1035	1261	1734	2032	-	-	-	Con
910	111	-	-	518	-	561	688	706	793	948	1223	-	-	-	230
101	1273	-	-	514	-	566	701	887	934	1232	1707	-	-	-	1640
-	1101	-	-	518	-	-	-	716	-	910	-	-	-	-	2110
-	-	-	-	520	-	-	-	-	-	920	-	-	-	-	1701
-	Present	-	-	Neg	-	-	-	-	-	Present	-	-	-	-	Con

two weeks. In the first experiment the pancreatitis was produced by ligation and dissection of the pancreatic ducts. This at the same time assured the complete absence of pancreatic enzymes from the gastrointestinal tract on the occasion of the second induced pancreatitis. The ligation of the thoracic duct after the first experiment was completed excluded the thoracic duct from transporting enzymes at the time of the second experiment. This second pancreatic trauma was produced by injection of bile into the pancreatic ducts of a dog whose pancreatic enzymes thus had access to the body only through the blood stream.

Intravenous sodium pentobarbital, inhalation ether and 1 per cent procaine locally were selected as anesthetic agents to be used separately. Blood for serum amylase determination was drawn from the femoral vein and artery immediately before and after anesthetization. Urine specimens were obtained at thirty minute intervals for amylase determination.

Using sterile technique the peritoneal cavity was opened and blood was taken from the aorta and from small venous and arterial vessels of the pancreas. In three animals the portal blood was similarly studied. An attempt to minimize trauma to the pancreas until these specimens were taken was successful due to the presence of a pancreatic mesentery in the dog. The pancreatic ducts were then ligated at their duodenal orifice necessitating considerable pancreatic trauma. A nonabsorbable ligature was used. Blood specimens were then taken from the aorta and the pancreatic and portal veins at regular intervals for one hour (Table I). At the completion of the abdominal operation the thoracic duct was ligated at its venous outlet in preparation for the subsequent experiment. Again a nonabsorbable ligature was used. Several of the dogs required parenteral glucose and saline as postoperative supportive therapy.

Seven to ten days after the first operation the laparotomy was repeated. Pancreatic trauma was produced this time by the injection of 20 cc of sterile bile into the pancreatic ducts.

Blood and urine collections were repeated as in the first procedure. The dogs were sacrificed immediately postoperatively, and by careful dissection the occlusion of the pancreatic and thoracic ducts was checked. Specimens of duodenal, ileal and colonic contents were obtained for amylase analysis.

The amylase concentration of the serum was determined by a modified Somogyi method²³ and concentration expressed in Somogyi units per 100 cc of serum. Each concentration listed represents an average of two or three titrations.

RESULTS

The concentration of amylase in the serum rose rapidly even though the pancreatic and thoracic ducts were obstructed (Fig 1).

The concentration of serum amylase increased approximately 100 per cent in the femoral vessels within the first hour following the production of a bile pancreatitis. At the same time the concentration of amylase in the urine (Fig 1)

²³The modification consisted of incubation of starch with serum for 10 minutes instead of thirty minutes.

Concentration of Amylase in Serum of Pancreatic Artery (aorta) Pancreatic & Femoral Veins after Production of Experimental Pancreatitis

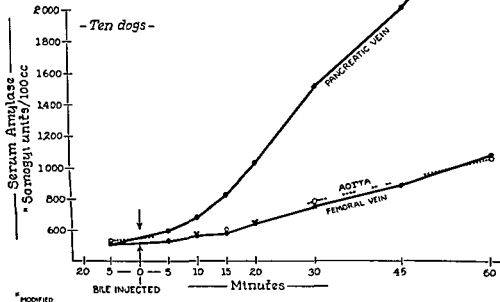
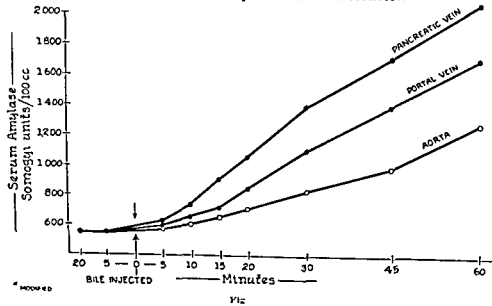


Fig 1

Concentration of Amylase in Serum of Pancreatic Artery (aorta) Pancreatic & Portal Veins after Production of Experimental Pancreatitis



two weeks. In the first experiment the pancreatitis was produced by ligation and dissection of the pancreatic ducts. This at the same time assured the complete absence of pancreatic enzymes from the gastrointestinal tract on the occasion of the second induced pancreatitis. The ligation of the thoracic duct after the first experiment was completed excluded the thoracic duct from transporting enzymes at the time of the second experiment. This second pancreatic trauma was produced by injection of bile into the pancreatic ducts of a dog whose pancreatic enzymes thus had access to the body only through the blood stream.

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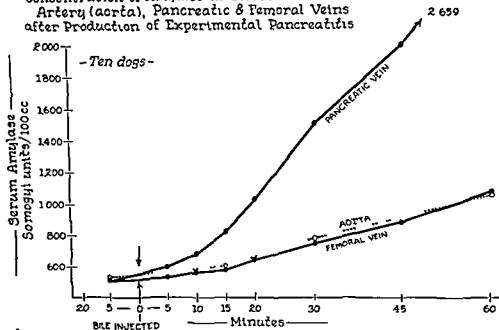
RESULTS

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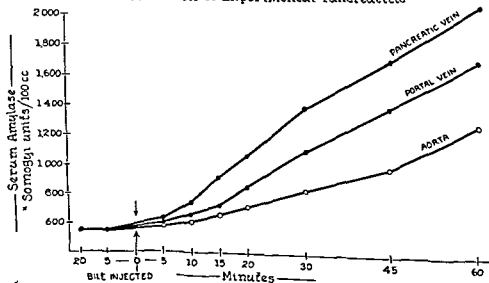
The concentration of serum amylase increased approximately 100 per cent in the femoral vessels within the first hour following the production of a bile induced pancreatitis. At the same time the concentration of amylase in the serum of the pancreatic veins increased approximately 500 per cent (Fig 1). An intermediate concentration was found in the portal vein (Fig 2).

²³The modification consisted of incubation of starch with serum for fifteen minutes instead of thirty minutes.

Concentration of Amylase in Serum of Pancreatic Artery (aorta), Pancreatic & Femoral Veins after Production of Experimental Pancreatitis



Concentration of Amylase in Serum of Pancreatic Artery (aorta) Pancreatic & Portal Veins after Production of Experimental Pancreatitis



Comparison of the concentration of amylase in the aortic blood serum and in blood serum from the veins of the damaged pancreas reveals a much higher concentration in the venous blood serum

As the serum level rose above an individual threshold, amylase appeared in the urine

Analysis of the specimens of duodenal ileal, and colonic contents revealed the absence of amylase seven to ten days after the ligation of the pancreatic ducts. In no instance was there gangrene of the bowel

DISCUSSION

Comparison of the concentration of amylase in the serum of the artery and vein of the pancreas before trauma reveals values which are almost equal. However, following trauma the concentration in the venous serum of the pancreas is much higher than in the arterial serum. In the absence of amylase in the gastrointestinal tract in the latter experiments this shows conclusively that the damaged pancreas is the main source of the additional enzyme.

In view of the autopsy findings of obstruction of the thoracic duct and of all of the pancreatic ducts and in the absence of amylase in the saliva and in the intestinal tract the high concentration of amylase reached in the serum from the pancreatic veins and reflected in that from the femoral vessels must represent release of the enzyme from the traumatized pancreatic cells into the surrounding tissues and absorption directly into the blood stream. As shown by the work of Popper and Necheles¹ lymphatic absorption plays a secondary role. That the direct blood stream absorption is the route by which amylase enters the serum of the patient with acute pancreatitis has not been proved but such an inference seems to be a definite possibility.

The very high levels in serum from the pancreatic vein and the portal vein are interesting in comparison with the concentration in serum from femoral vessels as the concentration in the serum of the extremities has been used in experimental and clinical studies. Similarly trypsin and lipase may be concentrated in the pancreaticoportal system following pancreatic trauma. It is possible that one or more of these enzymes is toxic to the liver in high concentration. Indeed the toxemia of pancreatitis might well be due in part at least to such a secondary hepatic damage. This thesis that the enzymes in high concentration may be hepatotoxic has been previously suggested.²

SUMMARY AND CONCLUSIONS

Experimental pancreatitis in the dog produces an increase in the concentration of amylase in the serum. That the additional amylase enters the serum from the traumatized pancreas is shown by a much greater concentration of amylase in the serum of the pancreatic vein over that in the serum of the artery. The pathway of the enzyme into the blood stream into the blood stream from the damaged pancreas leads to the conclusion of Popper and Necheles¹

REFERENCES

- 1 Popper, H. L. and Necheles, H. Pathways of Enzymes Into the Blood in Acute Damage of the Pancreas. *Proc Soc Exper Biol & Med* 43: 70 1940
- 2 King, C. E. Studies on Blood and Urinary Amylase. *Am J Physiol* 35: 301 1914
- 3 Elmsa, R. The Variations of Blood Amylase During Acute Transient Disease of the Pancreas. *Ann Surg* 105: 319 1937

CLEFT LEFT UPPER LOBES AND THE SPLIT ANTERIOR BRONCHUS

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FOR nearly a century anatomists and pathologists have been aware of the fact that not infrequently the right lung may be divided into four lobes and the left lung into three—this quite apart from such bizarre anomalies as the lobe of the azygos vein, the cardiac lobe, and other variants classified and elaborated upon in the recent article by Foster-Carter (1946). Thus in Cruveilhier's *Traité* of 1865 there was a whole page of figures to be copied the next year in Henle's *Handbuch*. But apparently no attempt to analyze the extra lobe of the left lung was made until 1893 when Bowles presented a case of four right and three left lobes at a meeting of the Anatomical Society of Great Britain and Ireland. Fortunately the pathologist ofrompton Hospital was present and the Secretary recorded that after Lowles presented the ulcer that both lungs had two lower lobes, since the upper left must correspond to the right middle (according to Aclis). Dr Fawcett regarded the additional lobe in the left lung as derived from the upper lobe and as representing a middle lobe. William Fawcett knew what he was talking about, having a more profound knowledge of the bronchial districts than any contemporary investigator.

Subsequently Devé (1900) found three cases of middle left lobe in 180 infant lungs. On the ground that the supernumerary fissure was horizontal he correctly concluded that the extra lobe corresponded to the middle lobe of the right lung, and further his Fig. 2 (reproduced as Fig. 42 of Block's monograph, 1944) indicated that the fissure separated the lingular segments (B' and I') from the remainder of the upper lobe. He was incorrect, however, in assuming that Lowles' case was not that of a middle lobe merely because the fissure was oblique.

A third of a century later the brilliant young thoracic surgeon Nelson, not long before his untimely death, postulated that the occasional presence of true left middle lobe, plus the occasional occurrence of transverse fissures across the lower lobes (separating Devé's dorsal lobes from the basal segments) afforded strong evidence that each lung really consists of four primary divisions, a broad generalization which has received widespread acceptance.

However, except for the one specimen figured by Devé, no one seems to have recorded the bronchial content of such middle lobes. The matter was brought to my attention by the finding of eight left upper lobes cleft in four different ways in the last fifty dissected specimens. (In the first fifty analyzed by Boyden and Hartmann, 1946, no prominent extra measures had been

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cent it favors the upper division (Fig 5) and in 10 per cent it favors the lower division (Fig 6) Usually the trifurcate pattern is characterized by an accessory anterior bronchus ($B\lambda^2$) which buds out of the upper division (Figs 5 and 6), but in the 6 per cent of specimens in which the displaced anterior bronchus forks almost immediately (Fig 7) no room for the development of an accessory anterior bronchus seems to have been available

The reason for continuing to designate as B^2 the anterior bronchus that migrates to a new position while characterizing as $B\lambda$ the one that develops at the proper site is that the former almost invariably carries the important posterior ramus (B^2a) and is therefore considered to be the main anterior bronchus This brings us to a consideration of what I have termed the split anterior bronchus " a concept that was only partially envisaged in the earlier article

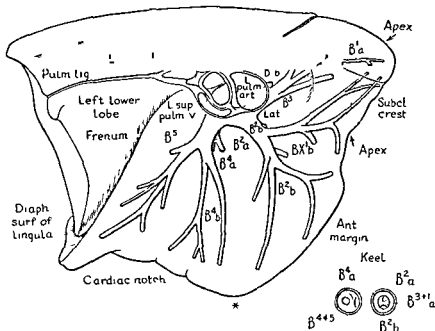


Fig —Specimen 91 illustrating the bifurcate pattern associated with the displacement of B^2 (11 per cent of specimens) Here B^2b arises as an accessory branch ($B\lambda^2b$) of B^2 in region B^2a the posterior ramus arises independently (see in cert) In this specimen B^2a arises directly from the lingular stem instead of from B^2 as in Fig 1 (15 per cent)

2 The Split Anterior Bronchus—The tendency for B^2 to be represented by two bronchi of separate origin is pronounced for an accessory anterior ramus ($B\lambda^2$) occurs in 15 per cent of 100 specimens (Table I item 2) Precursors of this pattern may be found in an additional 11 per cent of specimens in which B^2 forks almost as soon as it arises (Fig 7) From these con-

encountered) Curiously enough no two of these eight specimens were exactly alike (Plate 2 and Fig 3) Accordingly, it seemed desirable to analyze their bronchial content, but soon it became apparent that a more accurate determination of the normal limits of segments than was previously available would have to be made With this in mind the fifty specimens of Boyden and Hartmann were re-examined together with the second fifty recently made available† A description of the cleft lobes must thus be prefaced by a discussion of the varying limits of the segments particularly those of the anterior segment

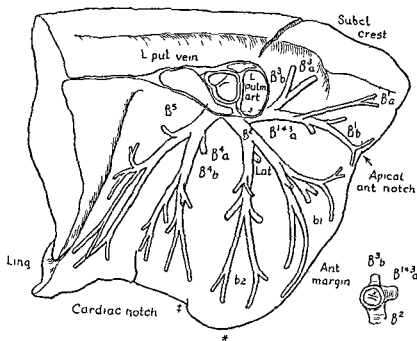


Fig 1—Specimen 58 illustrating the bifurcate pattern of the left upper lobe (73 per cent) and the prevailing pattern (6 per cent) in respect to the relations of apical and anterior bronchi. Upper division—B⁴a and B⁴b apical and anterior ramus of apical bronchus (B⁴) B⁴b anterior posterior ramus is absent in this anterior ramus of superior lingular anterior segment extending from the ramus in 38 per cent of 100 other angle of anterior margin.

1 The Prevailing Bronchial Pattern of the Left Upper Lobe—As illustrated in Fig 1 the prevailing pattern is bifurcate the bronchus subdividing into a superior and an inferior (or lingular) division This occurs in virtually three fourths (73 per cent) of 100 specimens‡ In the remaining 27 per cent the anterior segmental bronchus (B²) migrates inferiorly creating a trifurcate pattern In 7 per cent the orifice of P² is exactly central (Fig 11) in 10 per

†The writer is indebted to Dr Hartmann for having given this new material his critical attention and for authorizing me to state that the subsequent interpretations which modify a few details of our earlier work meet with his approval.

‡The earlier reported figure based on the fifty specimens of Boyden and Hartmann (1946) was 74 per cent.

the ramus labeled B^3 , in Fig 3 may be identified as the principal anterior bronchus

3 *The Varying Limits of the Anterior Segment*—If one examines the anterior margin of the left upper lobe (as seen in Fig 1) three landmarks appear upon which criteria of distribution can be based. The first is an indentation caused by the first rib (see dash line) and may be designated the *apical anterior notch*. Traced caudally from this point the anterior margin extends to a region of greatest curvature where it changes its direction markedly. This point may be referred to as the "*angle*" of the anterior margin. It is marked by an asterisk in all figures. From this angle the margin slopes into

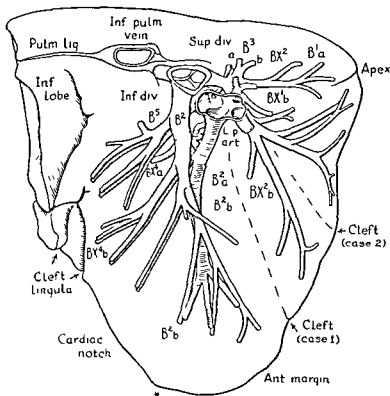


FIG 3—Specimen 9 illustrating ectopic position of left pulmonary artery (Lp art).
Dash line represents position of a supernumerary cleft in two cases. In case 1, the cleft is located in the anterior mediastinal region. In case 2, the cleft is located in the lingular region.

the shallow depression known as the cardiac incisure. This is often secondarily indented by small notches varying in number and position. Most constant is the *first notch of the cardiac incisure* († Fig 1). This first notch of Fig 1 (or a point correspondingly distant from the angle in other specimens) will be used as the third landmark. Incidentally this notch was the one re-

In all, three types of splitting have been encountered. The first (as recorded by Boyden and Hartmann, 1946) is associated with the trifurcate pattern. In this type space for the development of an accessory bronchus has been provided by the crural descent of the main portion of B^2 (as in Fig. 6). This occurs in twenty one out of twenty seven trifurcate cases (21 per cent of all specimens), in the remaining six a high and wide angled forking of the displaced B^2 prevented the development of BX^2 (Fig. 7).

TABLE I BRONCHIAL DISTRIBUTION TO ANTERIOR ZONE

1	Anterior zone supplied by a single bronchus (B^2)	6%
2	Anterior zone supplied by two separate bronchi (B and BX^2)	33%
(1)	B^2 and BX^2 both on upper division of lobar bronchus	19%
(a)	Trifurcate pattern. B^2 near center on upper division. BX^2 more distal on upper division (Fig. 5)	9%†
(b)	Bifurcate pattern. both B^2 and BX^2 distal to center but usually close together (Fig. 4)	10%
(2)	B central member of trifurcation. BX^2 distal on upper division	5%†
(3)	B^2 and BX^2 on different divisions of lobar bronchus	9%
(a)	" " " " " " " " " " " "	7%
(b)	" " " " " " " " " " " "	2%

†They total 91 per cent in this having a trifurcate pattern but

A second type previously figured in the 1946 article (E plate 1) but seen only three times and then without appreciation of its significance, represents *in situ* splitting of the anterior bronchus; both components usually remain in close together on the superior division of the left upper lobe stem (Figs. 4 and 10). It occurs in 10 per cent of specimens†. A precursor of this type may be seen in I₁₀, 13.

The third type is rare and newly recognized. It is associated with the occurrence of an ectopic left pulmonary artery (Fig. 3). In two out of three such anomalous specimens an enlarged inferior division of the left upper lobe bronchus bifurcated into an inferior lingular bronchus (B^3) and an anterior bronchus (B) the latter carrying its posterior ramus (B^{3a}). The superior division bifurcated into $B^2 + B^{2a}$ and an accessory anterior bronchus (BX^2) from which arose BX^{2b} (a displaced B^{3b}).

At this point one may logically ask on what basis has the bronchus labeled B^2 in Fig. 3 been identified as the main anterior segmental bronchus? Why for instance should it not have been called the superior lingular bronchus (P^4)? First, one may state that in the previously figured anomaly of this sort (illustrated by Fig. 6 of the 1946 article) the inferior division virtually broke up into three segmental bronchi: B , P^4 and B^3 although B^2 and B^3 had a very short common stem. The specimen shown in Fig. 3 is much like this except that here B^4 is a tributary of B^2 . More important however is the criterion of distribution. The limits of the territory supplied by B^2 have now been worked out in 100 specimens and in the light of this new information

†Two of these differed from the others in that PX^2 arose more distally

down" the stem of B² (Compare positions of B²b in Figs 1 and 2) In fact B²b becomes a stem of the second or third order† in 48 per cent of specimens (Boyden and Hartmann 1946)

Just as B²b may be easily identified because it distributes to the upper portion of the interlobar fissure, so L²b may be easily identified because it points toward the apical anterior notch, and if it has apical branches these usually approach the apex from the anterior side of the subclavian crest whereas the apical ramus (L²a) usually approaches the apex from the posterior side of the crest (Figs 2 and 4)

TABLE II ORIGIN OF THE ANTERIOR RAMUS OF THE APICAL BRONCHUS (B²b)

(1) Anterior ramus (B ² b) a branch of B ² and therefore entirely independent of the anterior bronchus (B)	100%
(a) Pifurcate pattern (B originates on upper division Fig 1)	55%
(b) Trifurcate pattern (B ² migrates inferiorly to	7%
(c)	38%
	15%
	20%

From the figures in Table II it is obvious that the displacement of B²b is primarily correlated with the trifurcate pattern since it occurs in about three fourths of such specimens but in only one fourth of the bifurcate specimens In further support of this correlation, it can be stated that in 27 per cent of specimens B²b, the accessory anterior ramus is associated with BX² the accessory anterior bronchus Apical and anterior bronchi thus frequently contribute to the formation of a new apical anterior bronchus

However, one might ask why the bronchus labeled BX² in Fig 5 should not be called B²b instead of BX The answer is that of thirty eight specimens having a BX² ramus associated with B² or LX the P² component is larger than the L² component in twenty one of these and that in twelve specimens they are equal whereas the B² component is larger in only five Accordingly it seems less confusing to use the term that fits the majority of cases In addition there is the progressive series of Figs 1 to 8 (omitting Fig 3) which shows the steps by which the anterior ramus of B² joins the anterior bronchus (B²) the way in which that portion of B² becomes split off and how the two halves move apart

5 *Miscellaneous Observations*—In concluding this section of the article occasion is taken to present certain supplementary data that were compiled in making dissections of the last fifty left upper lobes

The posterior ramus (L²a) of the anterior segment was found to be absent in 30 per cent of the last 50 as against 40 per cent of the first 50 thus making a total of 35 per cent for 100 specimens (that is an absence of the posterior ramus in one out of every three lungs)

The accessory posterior ramus (BX²a), arising from the lingular trunk was found in 14 per cent The incidence in the first 50 was 10 per cent, thus making a total of 12 per cent for 100 specimens

†Counting the upper and lower divisions of the upper lobe bronchus as the first order

ferred to by Churchill and Belsey (1939) as often marking the upper limit of the lingular segments

Employing these landmarks it has been ascertained that in 55 per cent of 100 specimens the caudal limit of the anterior segment is the first notch in the cardiac incisure († Fig 1). This is the prevailing pattern (see Brock Fig 49). In another 28 per cent it descends well beyond this point and may even reach as far as the lingula (Fig 11)† in another 15 per cent it retreats to the angle of the margin (Fig 2), and in 2 per cent it even fails to reach the angle.

Conversely, one may say that in 55 per cent of specimens the two lingular segments reach as high up as the first cardiac notch; that in 28 per cent they reach only halfway as far, or less; but that in 15 per cent they extend up to the angle of the margin and, in 2 per cent even beyond it (see Brock, Fig 56).

The cranial limit of the anterior segment (Fig 1) lies at approximately the apical anterior notch, sometimes a little to one side or the other of it. This is its situation in 56 per cent of specimens. The typical anterior segment may therefore be described as extending from the apical anterior notch to the first cardiac notch. This pattern is realized in 38 per cent of specimens (see Fig 1 also Fig 1 of the article by Scannell, 1947, based on gelatin injections of fresh specimens).

The remaining 44 per cent exhibit two major types of variations. The first group comprises the 11 per cent of specimens in which a displaced apical bronchus (B^1b) originates from the anterior bronchus (Fig 2 also Scannell's Fig 2), or from one of its rami (Fig 7). By virtue of this arrangement the anterior segment becomes greatly enlarged and may even extend from the apex to the first cardiac notch (see Fig 3 of the article by Scannell).

The second group comprises the 33 per cent of specimens (Table I) in which the main anterior segment (B) is reduced to one half its normal size (Fig 8), or even to a narrower zone (Figs 6 and 10), by the development of an accessory anterior bronchus (BX^2). Moreover since in twenty seven of these thirty three cases BX^2 carries a displaced apical bronchus (B^1b) the accessory anterior segment will usually have a greater length than the anterior proper. (Compare with Fig 4 of the article by Scannell.)

Of the two extremes, the greatly reduced and the greatly enlarged anterior segment the latter (that is B^2 carrying a displaced apical bronchus) is perhaps of greater clinical significance since it provides a bronchial pathway by means of which a diseased process in the apex can involve a major portion of the left upper lobe.

4 *The Variable Apical Bronchus (B^1)*—As a corollary to the preceding discussion attention should be called to the marked tendency of the anterior branch of the apical bronchus (B^1b) to 'slide down' onto the anterior bronchus (either B or BX^2). This occurs in 38 per cent of 100 specimens (Table II, item 2). (A comparable displacement of B^1b has been noted in 28 per cent of right upper lobes Boyden and Scannell 1948.) It may be compared to the tendency of B^1b (the posterior ramus of the posterior bronchus) to 'slide

†Anatomically the lingula is the "little tongue" that projects onto the diaphragm. The term is incorrectly used to indicate both lingular segments. Usually the lingula is the termination of B^2 while B^1 reaches the margin between the lingula and the first notch of the cardiac incisure.

Such specimens usually have an extra ramus to supply the new area. Superiorly the anterior bronchus has split into two components the upper of which BX², has an apical anterior distribution. In the second specimen (No 99), BX² has only an anterior distribution.

The second type (Figs 11 and 12) constitutes what may be called a *compressed middle* (or lingular) *lobe*. In Fig 11 the inferior lingular segment is well developed and the superior is represented by at least the posterior ramus (B'a). If the ramus labeled B'b represents the anterior component of B' then the lingular segments belong in that 12 per cent of specimens in which B'a is a branch of the lingular division of the upper lobe bronchus (Lloyd and Hartmann 1946). If B'b is correctly identified then it is reduced in size since most of it terminates in the lingula. Compression of the lingular segments seems to have been accomplished by expansion of the anterior segment (I²) and migration of its bronchus to a central position this being a true trifurcate pattern.

In Fig 12 I'b is rudimentary and B'a again originates from the lingular stem. In addition the lingular segments are fused to the lower lobe at the border of the supernumerary fissure and in this region P'a sends a substantial ramus to the upper half of the anterior basal segment (BX 1). Again the defective size of the lingular segments seems to be associated with hyperdevelopment of the anterior bronchi. The pattern is trifurcate and characterized by splitting of the anterior bronchus. The main stem (I² with its posterior ramus I 1) has shifted inferiorly but slightly favors the upper division side (see insert). The accessory bronchus (PX 1) is large and carries BX'b the displaced anterior ramus of the apical bronchus.

The third type represented by Figs 13, 14 and 15 may be called the *enlarged middle* (or lingular) *lobe*. In Fig 13 the extra lobe has expanded in both directions. Inferiorly it extends to the diaphragm and is partly fused to the lower lobe. (See interlobar fissure on diaphragmatic surface). Superiorly the upper lingular segment (B') extends to the angle of the anterior margin and in addition it carries a BX 1 the displaced posterior ramus of the anterior segment. Interestingly enough this straddles the supernumerary fissure.

A similar termination of B' appears in Fig 14. In fact B'b reaches so high in the lobe and B' is so much smaller that one is tempted to consider that I' represents a displaced I'. However its keel lies 15 mm below the keel which separates the lingular division from lower lobe bronchus (note anomalous arrangement of orifices) and no other migrating P² on the lingular side has had its keel deeper than 9 mm (most of them being 3 to 6 mm). For this reason and to avoid confusion high superior lingular bronchi with the inferiorly displaced anterior bronchi of the trifurcate type the bronchus in question has been designated I'. But very likely it represents a transitional form.

The posterior ramus (B^a) of the superior lingular bronchus arose directly from the lingular division (Fig 2) instead of from B¹ (Fig 1) in 18 per cent (as against 12 per cent in the first 50 specimens) thus making a total of 15 per cent in 100 specimens. Adding these to the displaced BX² group we find a displaced posterior ramus arising proximally from the lingular stem in 27 per cent of 100 specimens.

The lingular segmental arteries (A¹ and A²) were found to be wholly posterior in origin in 70 per cent, as previously recorded; they were wholly anterior in 10 per cent as against an earlier 8 per cent, the total for 100 being 9 per cent. They were of mixed origin occurring on both anterior and posterior surfaces in 21 per cent.

Three specimens having ectopic left pulmonary arteries were encountered (see Fig 3) as against none in the first 50 (omitting the one found soon after the first 50 specimens were dissected). Altogether, however, a total of 4 per cent were noted in approximately 100 specimens.

Of special interest are the new observations on the inferior limit of the left upper lobe. It was observed that while in the majority of specimens (56 per cent) the medial end of the lobe was attached to the upper end of the pulmonary ligament in the vicinity of the inferior pulmonary vein—either slightly above it slightly below it (Fig 7) or at the vein (Fig 2)—there was a significantly large number of specimens in which the medial end extended halfway from this point to the diaphragm (8 per cent, for example Fig 3), three fourths of the way (12 per cent, for example Figs 4 and 8) or even as far as the diaphragm itself (24 per cent, for example Figs 9, 10 and 13)†. There was congenital (as contrasted with pathologic) fusion in 24 per cent of the specimens but in only 4 per cent were bronchi of the upper lobe observed to supply anterior or medial basal segments of the lower lobe (see BX^a Fig 12). In previous dissections of the left lower lobe (Ierg, Boyden and Smith 1949) two other instances (4 per cent) were noted in which the converse was true namely that a basal bronchus (B³) supplied the fused area of the inferior lingular segment (I³).

Finally 8 instances of deeply cleft left upper lobes were found in the first 50 specimens (as against none in the first 50). Soon afterward a doubly cleft specimen was noted (Fig 15) making a total of 9 cases of 'middle lobe' in approximately 100 left lungs.

THE LEFT LEFT UPPER LOBE

Having established the criteria for recognizing the limits of a given segment it is now possible to analyze the middle lobes in these anomalous cases. They fall into four categories.

The *first type* (Fig 10) may be designated a *true middle* (or lingular) *lobe* since the bronchial elements of the lingular division are complete and the size of superior and inferior lingular segments (B¹ and B²) is normal. In this respect it resembles Dev's Fig 2 (Brock's Fig 42). Incidentally this is one of those cases in which the inferior lingular segment is continued to the diaphragm and incompletely fused with the lower lobe (see interlobar fissure).

†It should be recalled that in addition to this abnormal extension of the lower lobe along the pulmonary ligament the lingula has a diaphragmatic surface in almost all specimens.

EXPLANATION OF PLATE 2

(Drawings rendered for publication by Lawrence B. Benson)

This series of accurate sketches of cleft left upper lobes is designed to show the varying content of the so-called middle lobe of the left lung and the varying position and direction of the supernumerary fissure. The asterisk (*) marks the angle of the anterior margin a necessary landmark for interpreting patterns (see Fig 1). As in Plate 1 the yellow color designates the anterior bronchus or its two separated components B and B¹.

Fig 10—Specimen 96 illustrating a true middle lobe consisting of normal lingular segments separated from the upper division segments by a nearly horizontal supernumerary fissure. Additional features of this specimen are (1) an in situ splitting of the anterior bronchus (see Fig 4) and (2) extension of the inferior lingular segment to the diaphragm. The keel separating B¹ and B² lies 9 mm. below the main keel (that which separates upper and lower divisions of the upper lobe bronchus).

Fig 11—Specimen 9 illustrating the "compressed lingular" type of middle lobe. The bronchial elements of the lingular segments are present although arranged in lateral and medial zones as in the right lung also B² as occasionally happens (Fig 9) is a posterior branch of the lingular division rather than of B itself. The striking features of this specimen are the atypical expansion of the anterior segment (B¹) the displacement of its bronchus to form the middle member of a trifurcate upper lobe bronchus and an oblique supernumerary fissure.

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Fig 11—Specimen
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Fig 14—Specimen 85 illustrating a transitional type of expanded middle lobe. This might be considered to have been formed by cleavage of the space between the two components of a split anterior bronchus (see Fig 8). In other words the bronchus designated B could well be a transitional type. Together since to-
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relations seems better to consider the bronchus in question as a high B rather than a greatly displaced I. Illustrating the

Fig 15—This was a specimen which appeared after the first hundred left lobes had been dissected. Being carcinomatous its bronchi could not be followed peripherally but it has two superior and oblique fissures representing another transitional type. (See discussion under Fig 13). The keel separating B¹ and B² lies 1 mm. below the main keel.

EXPLANATION OF PLATE 1

(Drawings rendered for publication by Lawrence B. Benson)

This series of accurate sketches of uncleft specimens is arranged to show the progressive steps in the splitting of the anterior segmental bronchus (L^1) and the separation of its two components (indicated by yellow color). It is the basis for interpreting the cleft lobes shown in Plate 2.

Fig 4—Specimen 98 illustrating the in situ splitting of the anterior bronchus (10 per cent of specimens). For precursor stage see B. Fig 13. The lower component carries the clinically important posterior ramus (B^1a) and so retains the designation of the parent bronchus (B^1). The upper component now called the accessory anterior bronchus (B^1X) carries an accessory apical ramus (B^1Xb). Also in this case the splitting of B^1 without the downward migration of its main component has permitted an upward expansion of B .

Fig 5—Specimen 71 illustrating the downward migration of the lower component (B) to form a trifurcate pattern. As seen in the insert, the orifice of B is still on the upper division side the keel separating it from the rest of the upper division lying 4 mm below the main keel (that is the one separating upper and lower divisions of the upper lobe bronchus).

Fig 6—Specimen 9, illustrating further migration of the lower anterior component (B^1) so that its orifice now lies on the lower division side of the trifurcation. The keel separating it from the lingular bronchi lies 4 mm below the main keel.

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EXPLANATION OF PLATE 1

(Drawings rendered for publication by Lawrence B. Benson)

This series of accurate sketches of uncleft specimens is arranged to show the progressive steps in the 'splitting' of the anterior segmental bronchus (B) and the separation of its two components (indicated by yellow color). It is the basis for interpreting the cleft lobes shown in Plate 2.

Fig. 4 — Anterior view of specimen 71. The main bronchus (B) is shown splitting into two components, B¹ and B². B¹ is the upper component and B² is the lower component. The distance between the orifice of B¹ and the main keel is 4 mm. The distance between the orifice of B² and the main keel is 9 mm.

Fig. 5 — Specimen 73 illustrating the downward migration of the lower component (B²) to form a trifurcate pattern. As seen in the insert the orifice of B² is still on the upper division side the keel separating it from the rest of the upper division lying 4 mm. below the main keel (that is the one separating upper and lower divisions of the upper lobe bronchus).

Fig. 6 — Specimen 95 illustrating further migration of the lower anterior component (B²) so that its orifice now lies on the lower division side of the trifurcation. The keel separating it from the lingular bronchi lies 4 mm. below the main keel.

Fig. 7 — Specimen 100 illustrating the same pattern as Figure 6 but here the accessory anterior bronchus (B³) is 9 mm. below the upper lobe bronchus. The distance between the orifice of B³ and the main keel might have resembled that of B² in Figure 6.

The trifurcate pattern of the upper lobe bronchus occurs in 27 per cent the anterior bronchus (L^3) being exactly the middle member of the tripod in 7 per cent but favoring upper or lower divisions in the remainder (10 per cent each)

On the basis of more accurate determination of the limits of the anterior segment—which places the inferior (caudal) limit at the first cardiac notch in 55 per cent of 100 specimens and the superior (cranial) limit at the apical anterior notch in 36 per cent—it appears that the anterior segment occupies approximately the territory between these two notches in only 38 per cent of specimens. In the remainder the segment spreads upward or downward as a result of two processes

The first of these is a splitting of the anterior bronchus that is to say two bronchial buds arise from different sites on the embryonic tree to supply the territory of the anterior segment. The lower one carries the clinically important posterior ramus (P^1) and therefore retains the designation L^3 . The upper one (often the lesser and curving no posterior ramus) is called the accessory anterior (AX) although it originates from the usual site of the anterior bronchus on the upper division stem

This accessory anterior bronchus (AX^2) occurs in 33 per cent of 100 specimens and falls into three types. The first (21 per cent) is associated with the trifurcate pattern of the upper lobe bronchus in these specimens the lower of the two anterior buds arises from a central position. The second type (10 per cent) represents an in situ splitting of L^3 both buds remaining on the upper division. The third type (2 per cent) is rare being associated with ectopic pulmonary artery

A consequence of this splitting of the anterior bronchus is that the anterior segment proper is reduced in size and often thrust caudally out of position compressing in turn the lingular segments

A second process which also changes the size of the anterior segment is the downward displacement of the anterior ramus of the apical bronchus (B^3b). In 38 per cent it becomes an accessory anterior bronchus (AX^1) originating either on the anterior bronchus proper (11 per cent) or on the accessory anterior bronchus (27 per cent). In the former case it greatly enlarges the size of the anterior segment and is of clinical significance in that it provides a bronchial pathway by means of which a diseased process in the apex may involve a major portion of the left upper lobe. In the latter case it combines with the split off portion of the anterior segment to form an enlarged accessory anterior segment (AX) that is larger than the reduced anterior segment proper (L^3)

Applying these new observations to the problem of the cleft upper lobe it may be stated that the 8 per cent of left lungs exhibiting a middle lobe fall into four categories: (1) the true middle (or lingular) lobe (2 per cent); (2) the compressed middle (or lingular) lobe (2 per cent); (3) the expanded middle (or lingular) lobe (2 per cent); (4) the ectopic arterial type (2 per cent) in which the supernumerary fissure lies between B^3 and AX or between P^1 and the remaining bronchi of the upper lobe

In Fig. 15, the main supernumerary fissure is like that in Fig. 14 but there is still another fissure which partially separates the two lingular segments. Unfortunately the lung was so carcinomatous that the bronchi could not be dissected peripherally but obviously the superior lingular segment (B^4) terminates above the "angle" of the anterior margin. This specimen also represents a transitional pattern suggesting a split anterior bronchus but since the keel between B^4 and B^3 is 12 mm. below the keel separating upper and lower divisions the bronchus which supplies the "angle" has been conservatively designated B^4 †.

The fourth type, represented by dash lines labeled "case 1" and "case 2" in Fig. 16, may be named the *ectopic arterial type* since the cleft is presumably the result of the ectopic position of the left pulmonary artery. When called to my attention by students these two specimens had been so completely dissected that adequate drawings of the whole left lung could not be made for publication but the relation of the supernumerary clefts to the bronchi was clear. Accordingly the position of the clefts was added to a third specimen in which all details were complete.

Obviously the extra lobes in these two specimens are not lingular lobes since each contains the main anterior bronchus (I). In "case 1" the cleft developed between the anterior bronchus (I) and the accessory anterior bronchus (IX). As in Fig. 3, the inferior division of the upper lobe bronchus bifurcated into I^1 and I^2 , with B^4 represented by displaced rami which are branches of I^2 . Earlier in this article reasons for identifying B^4 as such were presented.

The second case differed from the first in that there was no accessory anterior bronchus (IX). Accordingly the cleft separated the apical posterior trunk (B^{1+2}) from the other bronchi of the lobe (I^2 , B^4 and B^3).

It is conceivable and even probable, that fissures may develop at these sites in the presence of a normally placed pulmonary artery, but at least the two cases listed here provide a fourth example for Foster-Carter's category of abnormal fissures that arise in association with displaced blood vessels—the others being the azygos vein, an abnormal ramus of the thoracic aorta and the subclavian artery.

In concluding this section it is clear that the so-called "middle lobe" of the left lung, while usually corresponding to the middle lobe of the right lung is not a consistent structure but may vary considerably in its bronchial content.

SUMMARY

Dissection of fifty left upper lobes in addition to the fifty previously described by Boyden and Hirtmann (1946) has revealed certain new features as well as permitting the study of variations to rest upon the broader base of 100 specimens.

EXPERIMENTAL TENDON REPAIR WITHIN THE FLEXOR TUNNELS USE OF POLYETHYLENE TUBES FOR IMPROVEMENT OF FUNCTIONAL RESULTS IN THE DOG

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PRIMARY tendon repair is a subject of universal interest. The general practitioner as well as the specialized hand surgeon find in it common problems. Both are interested in obtaining good function following repair. Both realize that many factors influence their results: the time interval between accident and repair, the degree of trauma to superficial and deep structures, the degree of contamination at the time of injury, the surgical technique employed, and lastly, yet perhaps most important, the location of the injury. All other things being equal, the degree of functional recovery following primary tendon suture can be predicted from the location of the injury. With clean wounds, early repair and careful surgical technique, good to excellent functional results usually follow primary tendon repair of the extensors and also of the flexors if the transection of tendon occurs in the forearm, wrist, proximal palm, or distal inch of the finger. However, if a flexor tendon is severed in the proximal two thirds of the finger or the distal inch of the palm, there is usually minimal return of function. Bunnell¹ calls this the "no man's land" of tendon repair and stated: "Severance of flexor tendons in the proximal segment of a finger and distal inch in the palm is not only the most common injury but is followed by the poorest results. When the problem of repairing a flexor tendon at this site is solved, the repair of all tendons will be comparatively easy."

It is with this particular problem that we are concerned. The reason for the minimal return of function following primary suture in this region is due to the anatomy of the flexor mechanism in the finger. The flexor profundus, flexor sublimus, and their common synovial sheath are enclosed in a snug-fitting fibrous tunnel in the region overlying the proximal phalanx. If it were not for the lubricating action of the synovial fluid, it is doubtful whether the tendons would be able to move at all in this area. Trauma in this region, which results in even minimal scarring, greatly impairs the gliding mechanism of these closely apposed structures. A major injury, such as laceration of a tendon, plus the subsequent trauma of surgical repair, is all too often followed by complete breakdown of the gliding mechanism. In its place, immobile adhesions form, binding tendons, sheath, and tunnel into a dense, adherent mass. Unfortunately, this is the end result in the majority of cases despite the most careful of traumatic techniques, and is always the end result when there is any deviation from strict asepsis, careful hemostasis, or gentle handling of tissues.

Other workers besides Bunnell stress the poor prognosis of tendon repair within the osseofibrous tunnels. Coates² stated: "(I) have never heard of a

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Supplementary observations on a few other points are appended

The posterior ramus of the anterior segment (B a) is absent in 35 per cent of 100 specimens

The accessory posterior ramus (BX²a, arising from the lingular trunk) occurs in 12 per cent of 100 specimens

The displaced posterior ramus (B⁴a) of the superior lingular bronchus arises from the lingular stem (instead of from the superior lingular bronchus) in 15 per cent of specimens. Adding this to the LX² a group displaced posterior bronchi arise on the lingular stem in 27 per cent of 100 specimens

The displaced posterior ramus (BX²b) of the posterior bronchus arises from the anterior bronchus (B² or BX) in 4 per cent of specimens

The lingular arteries (A⁴ and A³) are of wholly posterior origin in 72 per cent of wholly anterior origin in 9 per cent, and of mixed origin in 19 per cent of 100 specimens

Of special interest are the new observations on the inferior limit of the left upper lobe at the pulmonary ligament. In 56 per cent of 50 specimens it lies at approximately the level of the inferior pulmonary vein (either slightly above, below, or at the vein). In 24 per cent the upper lobe extends to the diaphragm, in 12 per cent three fourths of the way, and in 8 per cent one half of the way. In 24 per cent nearly one half of these inferiorly extended lobes, there was congenital fusion of upper and lower lobes in the inferior lingular area. In 4 per cent the inferior lingular bronchus (B³) sent branches into the adjacent basal segments

REFERENCES

- Berg Roger M, Boyden Edward A and Smith Franklin A. An Analysis of Variations of the Segmental Bronchi of the Left Lower Lobe of Fifty Dissected and Ten Injected Lungs. *J Thoracic Surg* 18 216 230 1949
- Bowles Dr. Lung With Four Lobes. *Proc Anat Soc Gr Britain & Ireland, J Anat & Physiol* 28 271 1894
- Boyden Edward A and Hartmann J Francis. An Analysis of Variations in the Bronchopulmonary Segments of the Left Upper Lobe of Fifty Lungs. *Am J Anat* 79 321 360 1947
- Boyden, Edward A and Scannell, J Gordon. An Analysis of Variations in the Bronchovascular Pattern of the Right Upper Lobe of Fifty Lungs. *Am J Anat* 82 27 74 1948
- " With Special Preference to the Surgery over its Press. (Also Guy's Hosp Rep on Pulmonary Resection in Bronchiectasis) 1934
- " d 4, Tome II Splanchnologie Paris, 1900
- Dévé M F. Valeur du lobe supérieur du poumon gauche. *Bull et mém Soc Anat* 2 169 374 1900
- Foster C. " *Brit J Tuberc* 40 111 1946
- Hensle, Y. " *Handbuch der Anatomie des Menschen* Bd. 2 Lungeweide 1934
- Neuson J. " *Anat* 66 928 241 1932
- Idem. Postural Drainage of the Lungs, etc. " *J Anat* 79 321 360 1947
- Scannell J Gordon. A Study of Variations of the Bronchopulmonary Segments in the Left Upper Lobe. *J Thoracic Surg* 16 530 537, 1947
- Scannell J Gordon and Boyden Edward A. A Study of Variations of the Bronchopulmonary Segments of the Right Upper Lobe. *J Thoracic Surg* 17 232 250, 1948

was voiced by Koch,² who stated 'The nutrition of the tendon within the finger must come in part from the capillaries of the subcutaneous tissue which overlies it. Blocking off the ingrowth of blood vessels at the line of suture jeopardizes the sound healing of the sutured tendon ends which is the first essential to restoration of function.'

Despite the failure of other workers to prevent adhesion formation with their membranes and the possibility that good tendon healing requires the blood supply of the extratendon tissues we felt that the 'block' method offered enough promise for further investigation. In our study we hoped to accomplish three goals: (1) to find a suitable membrane for the 'block' technique (one that was inert in body tissue yet at the same time pliable and workable into tubes of varied length and diameter); (2) to prove experimentally whether or not tendons can heal strongly even though blocked away from the extratendon tissues, and (3) to show experimentally whether or not function following primary tendon repair within the flexor tunnel can be definitely improved by the use of the 'block' technique.

METHOD

The first step in the solution of our problems was the development of a well controlled experimental method. The experimental method must satisfy three criteria: (1) The anatomy of the flexor mechanism of the experimental animal and the human being must be essentially the same; (2) the experiment must be well controlled; (3) adequate standards and methods for determining union and function of the experimental tendons must be devised.

The dog's flexor mechanism in the forefoot is almost the exact anatomic and functional counterpart of that of the human hand. The profundus and sublimus tendons are enclosed in a synovial sheath both in the palm and the digit. The two tendons with their common sheath are enclosed in a tight fitting osseofibrous tunnel as they pass over the proximal phalanx. The sublimus splits and the profundus passes between the diverging slips at the junction of the proximal and middle phalanx. The middle pulley crosses the sheath and the profundus tendon at the midpoint of the middle phalanx (Fig. 1). All the components found in the human tunnel area (distal palm and proximal phalanx) that would contribute to posttraumatic adherence of the tendons are found in the same area in the dog.

All the slips of the canine flexor digitorum profundus are fused at the wrist. This makes it possible to weave a tension wire with a pull out loop through the common portion of the tendon and by so doing to relax all the distal slips of the tendon. Thus the investigator may do primary tendon suture on two or more tendons under exactly similar conditions utilizing one tendon for experiment and one or more tendons for control.

Two of the criteria are hence fulfilled: (1) The anatomy of the dog's flexor mechanism is the counterpart of the human and (2) the anatomy of the dog provides the ideal situation for well controlled experiment concerned with the distal slips of the flexor profundus in the forefoot. The establishment of standards for the measurement of union and function will be discussed subsequently.

case where a flexor tendon divided in its distal sheath has been restored to usefulness by suture. Teece⁴ was also quite pessimistic and stated "I have never seen a successful primary or secondary suture of a flexor tendon when the point of division is actually within the flexor sheath itself. Mouat stated "(My) twenty five years' experience in a city in which the local trades predispose to such injuries coincides exactly with that of Teece.

Statistical analyses of functional results following primary suture within the flexor tunnel are hard to find in the literature. One is led to believe that the reason for this is that poor results far outweigh the good ones. However, an exception to this is the very careful analysis by Miller⁵ of 300 cases of tendon repair done at the Detroit Receiving Hospital. Thirty one repairs were done on flexor tendons over the proximal phalanges. Twenty or 60 per cent of these repairs resulted in good function (80 per cent return of normal function), eleven or 40 per cent resulted in poor or nonfunctioning tendons. A more optimistic outlook was given by Posch,⁷ who reported twenty out of twenty six good to excellent results following primary tendon suture within the flexor sheath. It would be interesting to know how many of these repairs were done within the flexor tunnel the area in which the poorest results occur.

In summary it appears that primary tendon repair within the flexor tunnel is still the number one problem of tendon surgery.

In the past, the attempts toward the solution of this problem have been made from three directions: (1) perfection of surgical technique in the primary repair; (2) use of new reconstructive methods in secondary procedures; (3) attempts to block the formation of adhesions by wrapping the tendon and excluding the anastomosis from the extra tendon structures by means of organic and inorganic membranes.

The greatest amount of clinical effort has been directed toward the refinement of delicate atraumatic techniques in the primary repair of the tendons. Bunnell,⁶ Koch,⁸ Mason⁹ and Posch⁷ have all contributed to this field. Their results in the flexor tunnel however still do not compare with tendon repairs in other regions.

In many cases secondary procedures have been done in the attempt to overcome the bad results of the primary repair. Much experimental and clinical work has been done in this field. The use of the free tendon graft has been successful in some hands.¹⁰⁻¹² Mayer¹³ attempted to construct a new nonadherent sheath in order to achieve greater function in tendon grafting. Despite these efforts free tendon grafts become functional only in the best of hands.

The use of membranes in the form of tubes or wrappings around the repaired tendon with the hope of preventing adhesion formation has been advanced by many authors using many different types of membranes. Wilmoth¹⁴ advocated the use of tunka vaginalis. Davis¹⁵ experimented with beef amniotic membrane, beef allantonic membrane, sheets of catgut, beef uccum and cellophane. Wheelodon¹⁶ used cellophane in a clinical case. McKee¹⁷ implanted Vitallium¹⁸ tubes in experimental cases with subsequent removal of the tube. He also tried without outstanding success the use of the Vitallium tube in the wrapping of tendons.

sterile two inch tubular stockinet was placed over the toes and phalangeal foot pads. A longer (one foot) length of two inch stockinet was then placed over the entire exposed forearm.

The first operative step was the insertion of the tension wire. Over the medial aspect of the wrist, a two inch curved skin incision was made through the stockinet (see Fig 2). The skin edges were fixed to the cut edges of the stockinet by small Michel skin clips. The underlying superficial structures were isolated and retracted, the common portion of the profundus tendon mobilized and brought into the wound by passing a knife handle beneath it.

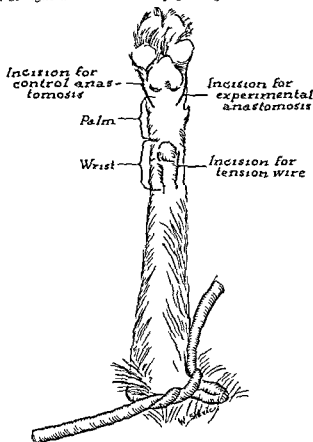


Fig. 2—Schematic sketch indicating the location of the three skin incisions. The *Palm* and *Wrist* indicate the regions in the dog which correspond to similar regions in the human being.

A No. 32 stainless steel tension wire with a proximal pull out loop was woven through the common portion of the tendon after the method of Bunnell.² The proximal pull-out loop and distal ends of the tension wire were brought through the skin through buttons fixed with shot, and tied over the shot. Fairly strong traction was exerted on the tension wire in order to relax completely the distal portions of the tendon.

The first operative problem to consider was the type of tendon suture to use. Bunnell's "suture at a distance" technique was chosen for several reasons. First it seemed logical that a technique leaving the least nonabsorbable suture material in the tendon would probably lead to minimal reaction and adhesion formation. Second, by placing the tension wire and pull out loop in the wrist both experimental and control tendons were relaxed with a single maneuver. Third, the clinical results obtained by Bunnell² utilizing this technique compared favorably with those utilizing other methods. This method was found to be extremely simple, quick, and completely satisfactory in the 190 experimental primary tendon anastomoses that were done in connection with this project.

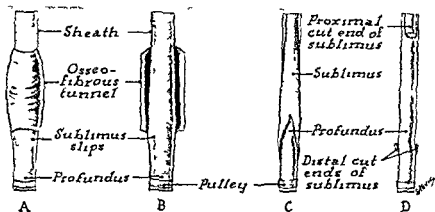


Fig. 1. Mechanism of the dog in the digits 1 to 4 of the human hand. (A) Superovital sheath intact. (B) The osseofibrous sheath is still intact. (C) The osseofibrous sheath has been transected distally. The profundus alone remains.

Mongrel dogs of either sex, weighing between 8 and 20 kilograms were used. Dogs weighing 15 kilograms or more were preferred because of the greater size of their tendons. The dogs with no preoperative medication were anesthetized by the intravenous administration of an aqueous solution of sodium nembutal (1 gr. per cubic centimeter) in a dose of 0.44 c.c. per kilogram. Placed on their backs on a dog operating table the volar surface of the wrist, palm and the outer aspects of the second (index) and fifth (little) digits were carefully shaved. The foreleg was made bloodless by an Esmarch bandage followed by a rubber tourniquet just above the elbow. The foreleg was fixed to a Mayo stand using a four foot loop of heavy string running from a cleve hitch about the muscular portion of the foreleg around the Mayo stand at right angles thus immobilizing the digit completely free. The shaved area was then carefully draped in order to expose the wrist to the toes. A cap of

mosquito clamps, and the suture tightened and tied. It was possible to obtain extremely accurate approximation with this method.

After the suture was completed the experimental tube was brought over the anastomosis. The edge of the tube was anchored to the lateral wall of the tunnel with a single suture of 0000 silk to prevent possible displacement.

For the control procedure a new skin incision was made over the lateral aspect of the fifth (little) digit, the tunnel opened, the sheath split, the sublimis excised, and the profundus transected. The cut ends were carefully approximated with the same basket weave suture of 0000 silk. No tube was used around this anastomosis.

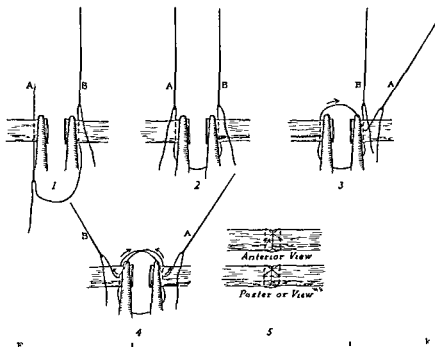
The skin clips were then removed and the skin incisions closed with interrupted vertical mattress sutures of 0000 silk. The tourniquet was released and two layers of serially wound sheet wadding were placed about the foreleg from toes to elbow. Three to four layers of plaster of Paris were then wrapped around the leg. A wide splint of leaded wire screen (1/2 inch square) was molded about the forearm and placed between the two outer layers of plaster. After the plaster had dried the cast was entirely covered with strips of adhesive tape.

Obtaining long periods of immobilization was found to be one of the most difficult technical problems. The dogs found it very easy to chew off ordinary plaster casts. Aluminum splints incorporated within the casts were not successful in preventing the early loss of immobilization. Plastic (Aire lite) casts were no better. The final system (padded plaster plus wire screening) was quite successful and these casts stayed on indefinitely. In my experience dogs would not tolerate unpadded plaster casts and even though such a cast was carefully applied a high incidence of pressure sores and secondary infections occurred.

After selected periods of immobilization the casts were removed. Tests for strength and function were performed at varying intervals thereafter. For these tests the dog was anesthetized and placed on his back on the animal operating table. The volar surface of the foreleg was shaved and scrubbed. The foreleg was rendered bloodless and new incisions were made over the fifth and second digits. The new incisions were longer than the original ones in order to mobilize the tendon slips in unoperated areas that is beyond the middle pulley distally and in the palm proximally. After the tendon had been freed in these areas longitudinal traction was applied to the proximal segment of the tendon and the excursion of the distal segment of the tendon carefully noted. The distal tendon was then transected above the pulley and traction again applied to the proximal segment of the tendon. If it were possible to withdraw the divided tendon the gross amount of pull was noted. If it were impossible to withdraw the tendon it was carefully dissected out. The tendon segments thus removed (by withdrawal or dissection) were then placed in a tensiometer (Fig. 4) in which it was possible to measure in pounds the pull necessary to break the sutured tendons. The tensile strength of the tendon was computed in grams per square millimeter (the cross sectional area of the tendon having been previously determined). It was impossible to break a few of the tendons with this apparatus. The tensile strength of these tendons was reported

The wrist incision was covered with sterile gauze to preclude contamination until the end of the procedure when all the skin incisions were closed. The scene of operation was then shifted to the digits.

A new incision was made over the lateral aspect of the second (index) digit (see Fig. 2). The volar surface of the osseofibrous tunnel, and the sheath and pulley distal to it were exposed. The sheath was incised distal to the tunnel but proximal to the middle pulley. The sheath and the volar surface of the tunnel were split longitudinally to the proximal end of the tunnel. The sublimus tendon was excised from the distal insertion of its diverging slips to the proximal end of the fibro osseous tunnel to eliminate the possibility of its adhering to the suture line.



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The free lying relaxed profundus was cut across with a knife in the middle of the tunnel. The experimental tube was then threaded over either the distal or proximal segment of the tendon. The free tendon ends were grasped with straight mosquito clamps and a single basket weave suture of 0000 braided silk (Fig. 3) was placed in the tendon ends just behind the clamps. The technique of placing this suture was modified from that of Bunnell² in that two needles one at each end of the suture were used. By this technique the twisting tendency of the one needle method was obviated. The tendon ends were then carefully cut across immediately behind the crushed tips of the tendons held in the

as stronger than the maximum reading and no further attempts were made to measure their actual strength. In the early part of the experiment the actual strength of a few tendons was not determined and only gross determinations of strength of union were made. This was done by attempting to break the tendon union by fixing clamps to each end of the tendon and exerting traction in opposite directions. If the union withstood vigorous traction, it was deemed strong and so reported. Other tendons were saved for microscopic examination and their union was similarly tested and reported. By these methods it was possible to obtain comparative values of strength of tendon union following primary suture within the flexor tunnels.

The derivation of a method for measuring function was far more difficult than for that of measuring strength. Ideally, one would like to measure the number of degrees of active flexion and extension of the digits in the normal dog and compare it to the experimental digits. Unfortunately, it was impossible to do this in the experimental animal since this necessitated voluntary action on the part of the animal. The next best procedure was to measure the passive excursion of the tendon within the digit plus the degree of adherence of the tendon within the tunnel and to compare these values with those found in the normal dog. In the intact normal dog the distal portion of the profundus tendon moved 3 to 4 mm when traction was applied to the palmar segment of the profundus tendon after cutting the tendon distally; it was impossible to withdraw it from the tunnel by traction applied proximally. If the sublimus was excised from the tunnel and the vinculum dissected away from the palmar segment of the profundus the distal portion of the tendon moved 3 to 8 mm when traction was applied proximally, and after cutting the tendon distally, it could be easily withdrawn from the tunnel.

Since in this experimental method the sublimus tendon was partially removed the profundus in this situation would normally have a distal excursion of 3 to 8 mm and if the tendon were transected distally it could easily be withdrawn from the tunnel. If the experimental tendon behaved in a similar manner it was graded as normal (3 plus function). Lesser degrees of function were graded as follows: 2 plus function 1 to 3 mm excursion of the distal tendon and the ability to withdraw the tendon from the tunnel after distal division of the tendon with moderate to strong traction applied proximally; 1 plus function 1 to 3 mm excursion of the distal tendon yet inability to withdraw the transected tendon from the tunnel; 0 function no excursion of distal tendon and inability to withdraw the transected tendon from the tunnel. In addition, an unhealed tendon was graded as having 0 function.

Thus function of the tendon following primary suture within the tunnel has been designated by objective functional grades ranging from 0 to 3 plus indicating the stages between nonfunction and normal function.

SUMMARY OF METHOD

(1) The anatomy of the flexor mechanism of the forefoot of the dog is essentially the same as that in the human hand and presents a situation ideal for well-controlled experiment. (2) A quantitative method for determining the strength and a system of grading function from 0 to 3 plus following primary

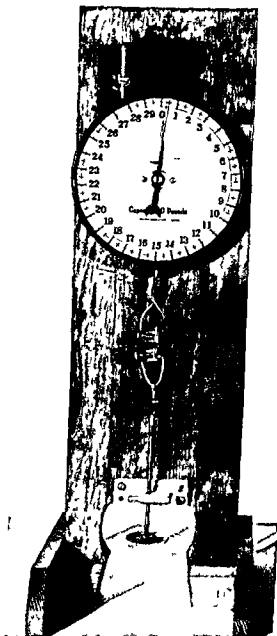


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used about tendons. No gross or microscopic reaction to the polythene was ever noted.

Polythene film proved to be a suitable material for use in the "block" technique because of its tissue inertness, flexibility, and its adaptability to tube manufacture.

2 *Healing of tendons within polythene tubes*—Twenty five profundus tendons were divided, sutured in the flexor tunnels and surrounded by polythene tubes (Table I). The suture lines were completely blocked away from the extra-tendon structures. The tendons were immobilized by tension wires and casts from eight to sixty five days. The tubes were left in place from twelve to seventy nine days. Not only did healing occur within the tubes but strong healing occurred when the period of immobilization was forty days or longer. A summary of the tensile strength of the tendons measured in grams per square millimeter, can be found in Fig. 5.

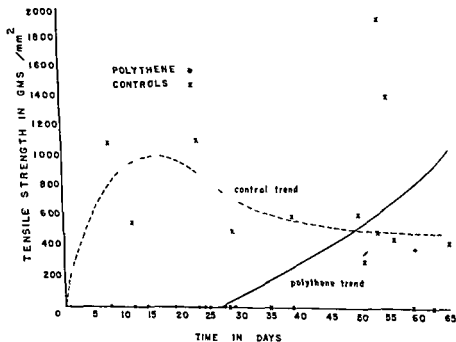


FIG. 5—Graph showing the relationship of strength of healing to the period of immobilization in the polythene blocked tendon repairs and in the controls.

As can be seen the control tendons healed much earlier than the polythene tendons. No tendon protected by a polythene tube healed before twenty nine days. After twenty nine days strength of union increased rapidly. The average tensile strength of polythene tendons immobilized forty days or longer was 785 Gm. per square millimeter. The average control tendon for the same period was 624 Gm. per square millimeter. These values demonstrate that if immobilization is prolonged strong healing does occur in blocked tendons. That these values are an indication of actual strong healing, is confirmed by

tendon repair within the flexor tunnels is described. (3) Primary tendon repair employing meticulous asepsis, bloodless field, atraumatic technique and plaster cast immobilization was accomplished by utilizing Bunnell's removable tension wire, a single (basket weave) suture anastomosis and experimental tubes to block the extratendon tissues. Every procedure was accompanied by a control.

EXPERIMENTAL RESULTS

I Search for experimental membrane suitable for use in the "block" technique—At first it was thought that absorbable materials would best be suited for this technique with the hope that the material would stay present long enough to prevent cross growth of adhesions and would then slowly melt away, obviating any necessity for a secondary removal of the material as was the case with metallic tubes. With this idea in mind gelatin was first tried. This material is a supposedly nonirritating, absorbable protein. It was possible to mold tubes from moistened sheet gelatin, harden the tubes in 10 per cent formalin and use these tubes in the "block" technique. Unfortunately, the gelatin tubes gave a marked tissue reaction with the formation of dense adhesions and were not suitable for our purpose. The failure of the gelatin tubes was probably due to the irritating qualities of the formalin used to plasticize them.

Cellulose acetate phthalate was next tried. This material is used commercially as an enteric coating for medications. Preliminary tests showed this material causes no tissue reaction. By plasticizing with 70 per cent alcohol it can be molded into tubes. Five tendons were blocked with phthalate tubes. However, the material was broken down too quickly (three days) for the tubes to function as a blocking mechanism.

Gelfoam and fibrin film tubes were similarly tried on seven tendons. These tubes also disappeared too soon to achieve the desired results. At this point absorbable plastics were abandoned in favor of nonabsorbable materials.

At about this time Grindley¹⁶ reported on a new substance, polyethylene film.* His work indicated that this material was singularly nonirritating in tissues. It was commercially available as film in varying thicknesses and as thick walled tubes. The film proved to be particularly adaptable for my work. Because of its low melting point tubes of thin (.003 inch) film edges. The tubes thus formed

prefabricated tubes were used about primary repairs. In secondary repairs after primary healing of the tendon, but where adhesions caused loss of function a tube was constructed at the time of operation by encircling the freed tendon with a single layer of film and heat sealing the clamped free edges. In the experimental series concerned with primary suture of the profundus tendon within the flexor tunnel standard tubes of .003 inch polythene film measuring 2 cm. in length and 4 mm. in diameter were used. Thirty polythene tubes were

* Commercially known as polythene. The materials used in this study were supplied by the Visking Corporation of Terre Haute, Ind. Polythene is a polymer consisting of chains of ethylene under high pressure. The result is a macromolecular consisting of long carbon chains in which each carbon bears two hydrogen atoms. Polythene may play a role in the paraffin in which the chain molecules are very much longer than in ordinary household paraffin.

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withdrawn	3+	3 mm movement of distal tendon can be easily withdrawn	3+	3 mm movement of distal tendon can be easily withdrawn	3+	3 mm movement of distal tendon can be easily withdrawn	3+	3 mm movement of distal tendon can be easily withdrawn	3+	3 mm movement of distal tendon can be easily withdrawn	3+	3 mm movement of distal tendon can be easily withdrawn	3+	3 mm movement of distal tendon can be easily withdrawn	3+	3 mm movement of distal tendon can be easily withdrawn	3+	3 mm movement of distal tendon can be easily withdrawn	3+	3 mm movement of distal tendon can be easily withdrawn	3+	3 mm movement of distal tendon can be easily withdrawn	3+	3 mm movement of distal tendon can be easily withdrawn	3+	3 mm movement of distal tendon can be easily withdrawn	3+	3 mm movement of distal tendon can be easily withdrawn	3+	3 mm movement of distal tendon can be easily withdrawn	3+	3 mm movement of distal tendon can be easily withdrawn	3+	3 mm movement of distal tendon can be easily withdrawn	3+	3 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TABLE I

NUMBER OF WEEKS IMMOBILIZATION	WT (IN KG.)	PERIOD OF IMMO- BILIZATION (IN DAYS)	PERIOD BETWEEN REMOVAL OF IMMO- BILIZATION & EXAM	TENDON STRENGTH (IN GM. IPR SQ. MM.)		TENDON FUNCTION			FEMUR TRAPEZOIDAL	FEMUR TRAPEZOIDAL
				CONTROL	POLY- THIENE	FINDINGS AT EXAM	FINDINGS AT EXAM	FINDINGS AT EXAM		
48 246	160	8	71	1111	0	No movement of tendon dense adhesions	0	0	0	Are lito cast used instead of plaster, accounts for early loss of immobilization
48 301	1425	12	0	567	0	2 mm movement of distal tendon, tendons can be with drawn from tunnel with strong traction	2+	0	0	Dog died, pneumonia, accounts for early exam
48 65	180	14	54	Good	0	2 to 3 mm transmittent movement of distal tendon, impossible to withdraw tendon	1+	0	0	
48 9	80	19	6	0	0		0	0	0	
48 16	80	22	7	0	0		0	0	0	
48 233	130	23	18	113	0	1 to 2 mm. transmittent movement of distal tendon, tendon can be with drawn with extreme traction	-+	0	0	
48 303	130	24	0	Strong	0	No movement of tendon, impossible to withdraw tendon	0	0	0	Tendon broke on withdrawal
48 13	100	25	9	Very strong	0	2 to 3 mm. transmittent movement of distal tendon, impossible to withdraw tendon	1+	0	0	
48 91	1525	28	19	0	0		0	0	0	Secondarily infected pressure sores

	48-50	18	1	10	100	104	to 3 mm trans mitted movement of distal tendon im- possible to with- draw tendon	1+	3 mm movement of distal tendon can be easily withdrawn	3+	Secondarily in- fected, cast force
46	48-23	16.5	30	2	0	2.0	Tendon broke on with draw	0	3 mm movement of distal tendon ten- don can be easily withdrawn	3+	
	48-00	14.3	31	0	100	100	3 mm trans mitted movement of distal tendon impossible to withdraw tendon	1+	3 mm movement of distal tendon, ten- don can be easily withdrawn	3+	
	48-207	15.0	39	-	0	0		0		0	
	48-100	13.75	41	0	Strong	Strong	No motion of distal tendon impossible to withdraw tendon	0	3 mm movement of distal tendon ten- don can be easily withdrawn	3+	Anastomosis, for sectioned for microscopic exam
	48-13	11.5	49	0	Strong	Strong	to 3 mm motion of distal tendon im- possible to with- draw tendon	1+	3 to 4 mm move- ment of distal ten- don, tendon easily withdrawn	3+	Anastomosis sectioned for microscopic exam
	48-208	15.3	51	0	610	1100	3 to 4 mm move- ment of distal ten- don, impossible to withdraw tendon	1+	3 mm movement of distal tendon, ten- don easily with- drawn	3+	
08	48-110	14.0	51	0	320	774	3 to 4 mm movement of distal tendon impossible to with- draw tendon	1+	3 mm motion of dis- tal tendon, tendon withdrawn with moderate traction	+	
	48-11	11.5	53	0	>1850	>1850	No motion of distal tendon impossible to withdraw tendon	0	to 3 mm motion of distal tendon ten- don easily with- drawn	3+	

(Continued on following page)

TABLE I

NUMBER OF WEEKS IN OBSERVATION	DOG NO	WT (IN KG)	PERIODS OF IMMOBILIZATION (IN DAYS)	PERIOD BETWEEN REMOVAL OF IMMOBILIZATION (EXAM)	TENDON STRENGTH (IN QM PER SQ MM)		TENDON FUNCTION			REMARKS	
					CONTROL	POLY THEVE	FINDINGS AT EXAM	FUNCTION GRADE	FINDINGS AT EXAM		FUNCTION GRADE
12	48 246	10.0	8	71	1111	0	No movement of tendon dena e adhe mona	0		0	Aire lite cast used instead of plaster ac counts for early loss of immo bilization
	48 301	10.5	12	0	067	0	mm movement of distal tendon, tendon can be with drawn from tunnel with strong traction	2+		0	Dog died, pneumonia, accounts for early exam
	48 08	19.0	14	54	(ood	0	to 3 mm. trans mitted movement of distal tendon im possible to withdraw tendon	1+		0	
	48 73	52.5	19	6	0	0		0		0	
24	48 10	20.0	22	7	0	0		0		0	
	48 033	13.5	3	18	1137	0	1 to 2 mm trans mitted movement of distal tendon tendon can be with drawn with extreme traction	2+		0	
	48 103	13.0	24	0	Strong	0	No movement of tendon impossible to withdraw tendon	0	Tendon broke on withdrawal	0	
	48 13	10.75	26	9	Very strong	0	to 3 mm. trans mitted movement of distal tendon im possible to withdraw tendon	1+		0	
	48 81	15.25	29	19	0	0		0		0	Secondarily infected pure sore

	48-50	18-19	30	10	000	04	to 3 mm transmittal movement of distal tendon, impossible to withdraw tendon	1+	3 mm movement of distal tendon, tendon can be easily withdrawn	3+
46	48 232	165	30	-	0	20	Tendon broke on withdrawal	0	3 mm movement of distal tendon, tendon can be easily withdrawn	3+
	48 60	143	39	0	500	000	3 mm transmittal movement of distal tendon impossible to withdraw tendon	1+	3 mm movement of distal tendon, tendon can be easily withdrawn	3+
	48 203	100	39	2	0	0	No motion of distal tendon, impossible to withdraw tendon	0	3 mm movement of distal tendon, tendon can be easily withdrawn	0
	48 106	110	47	0	Strong	Strong	No motion of distal tendon, impossible to withdraw tendon	0	3 mm movement of distal tendon, tendon can be easily withdrawn	3+
	48 203	110	49	0	Strong	Strong	2 to 3 mm motion of distal tendon, impossible to withdraw tendon	1+	3 to 4 mm movement of distal tendon, tendon can be easily withdrawn	3+
68	48 308	133	51	0	610	1100	3 to 4 mm movement of distal tendon, impossible to withdraw tendon	1+	3 mm movement of distal tendon, tendon can be easily withdrawn	5+
	48 110	110	51	0	330	704	3 to 4 mm movement of distal tendon, impossible to withdraw tendon	1+	3 mm motion of distal tendon, tendon can be easily withdrawn with moderate traction	2+
	48 110	130	53	0	>1890	>1950	No motion of distal tendon, impossible to withdraw tendon	0	3 to 4 mm motion of distal tendon, tendon can be easily withdrawn	3+

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TABLE 1—CONT'D

NUMBER OF WOUNDS IN LIGATION	WT (IN KG.)	PERIOD OF LIGATION (IN DAYS)	PERIOD BETWEEN REMOVAL OF TENDON & EXAM	TENDON STRENGTH (IN GM. PER SQ. MM.)		TENDON FUNCTION			REMARKS
				CONTROL	POLY THENE	FIXATION'S AT EXAM	PLN- TION GRADE	FINDINGS AT EXAM	PLN- TION GRADE
38 81	10.75	33	0	485	444	4 to 5 mm trans mitted movement of distal tendon im- possible to with- draw tendon	1+	4 to 5 mm move- ment of distal ten- don tendon easily with drawn	3+
45 15	14.5	34	0	Strong	310	3 mm trans mitted movement of distal tendon impossible to withdraw tendon	1+	4 to 5 mm move- ment of distal ten- don tendon with drawn with mod- erate traction	4+
45 15	20.45	33	0	1440	945	No motion of distal tendon, impossible to withdraw tendon	0	3 mm motion of dis- tal tendon tendon with drawn with mod- erate traction	4+
45 271	15.50	34	0	445	0	1 mm motion of di- stal tendon impos- sible to withdraw tendon	1+	Tendon broke on withdrawal	0
45 210	14.75	33	0	0	30	Tendon broke on withdrawal	0	2 to 3 mm motion distally tendon withdraws with mod- erate traction	2+
48 85	11.5	62	0	0	1111	Tendon broke on withdrawal	0	3 mm movement of distal tendon with drawn with mod- erate traction	2+
48 103	15.0	65	0	430	1100	No movement of dis- tal tendon impos- sible to withdraw tendon	0	3 mm movement of distal tendon easily with drawn	3+

comparison with the data presented by Mason and Allen²⁷ in their work on tensile strength of tendons following primary repair. The strongest union which they obtained was in tendons that were immobilized for three weeks and then allowed unrestricted activity for twenty days. The average tensile strength of these tendons was 751 Gm per square millimeter. My figure of 785 Gm per square millimeter for blocked tendons immobilized for forty days compares favorably with their best results.

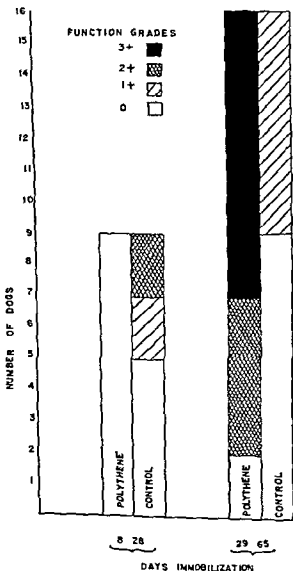


Fig 6—Bar diagram illustrating the functional results of tendon anastomosis blocked with polythene tubes as contrasted with the controls in terms of the period of immobilization.

In summary, flexor tendons in the dog do heal if blocked away from their extratendon tissues but healing is delayed. If immobilization is maintained forty days or longer, however, strong union results.

3 *Functional results with use of "block" technique*—The functional result of twenty five experimental tendons and twenty five control tendons were carefully graded according to the system described under Method. These functional results are summarized in graphic form in Fig. 6. The first two columns illustrate the functional results following twenty nine days or less immobilization. No polythene tendons healed during this time interval and therefore they all fall into the 0 functional classification. The next two columns however, illustrate the functional results following more than twenty nine days immobilization. Here fourteen out of sixteen polythene tendons achieved a functional rating of 2 or 3 plus while at the same time, not a single control tendon was rated better than 1 plus.

This data strongly suggests that function is greatly improved following primary suture in the flexor tunnels if the suture line is blocked away from the extratendon tissues by means of a polythene tube.

COMMENT

There are a few points other than those already discussed which were brought out during this work. One is the relation of immobilization to adhesion formation and resorption. From this work it is not possible to tell exactly when adhesions form, probably after twelve days but some very interesting points can be emphasized about their resorption and differentiation. "Mason and Allen" noted striking changes in the amount and the extent of adhesion formation in tendons immobilized for long periods of time. They stated "The gross appearance of tendons immobilized 45 weeks has direct practical significance. They were seen to be beautifully healed, the tissues about them were transparent and areolar and glided over the surface of the tendon and tendon itself glided through them." In the experiments reported here a similar differentiation of the extratendon tissues was noted in the control tendons that were immobilized for thirty five days or longer. The operative area in tendons immobilized for shorter periods of time was a solid mass of scar tissue. It was impossible to differentiate the tendon from the sheath or tunnel. However, following long periods of immobilization (thirty five days or more) there was a clear differentiation of the structures. The adhesions were filmy and translucent. It was easy to dissect the tendons away from the extratendon tissues. In the control tendons since the work was being done in the tunnels unlike Mason and Allen it was impossible to demonstrate free gliding of the tendons. Nevertheless this differentiation of tendon adhesions and extratendon tissues would argue for longer periods of immobilization than now advocated no matter what type of primary repair is employed.

The other point, really a suggestion is the possible use of polythene film about tendons that have healed primarily but are bound down by adhesions. After the adhesions have been dissected away from the tendon, polythene film could be wrapped about the tendon and thus prevent the infiltration of adhesions.

TABLE II SECONDARY WRAPPING OF HEALED TENDONS WITH POLYETHYLENE FILM

EXPERIMENTAL NUMBER	WT. IN KG	DAY 10 HEALIZATION FOLLOWING PRIMARY SUTURE	DAY 10 HEALIZATION FOLLOWING SECONDARY WRAP	TENDON STRENGTH (IN CM. PER SQ. MM.)		TENDON FUNCTION		FUNG TION GRADE	FINDINGS AT FINAL EXAM	FUNG TION GRADE	FINDINGS AT FINAL EXAM	FUNG TION GRADE
				CONTROL	POLYETHYLENE							
15-16	160	10	7	450	>1000	No movement of distal tendon, impossible to withdraw tendon	No movement of distal tendon, impossible to withdraw tendon	0	to 3 mm movement of distal tendon, impossible to withdraw tendon	0	to 3 mm movement of distal tendon, impossible to withdraw tendon	1+
19-20	200	15	18	66	0	No primary healing	No movement of distal tendon	0	Broke on withdrawal	0	Broke on withdrawal	0
19-21	230	32	7	>30%	340	to 1 mm movement of distal tendon with strong traction	to 1 mm movement of distal tendon with strong traction	+	3 mm movement of distal tendon, tendon withdrawn with mild traction	+	3 mm movement of distal tendon, tendon withdrawn with mild traction	3+
19-27	130	11	40	700	3,000	No movement of distal tendon, impossible to withdraw tendon	No movement of distal tendon, impossible to withdraw tendon	0	3 mm movement of distal tendon withdrawn with mild traction	0	3 mm movement of distal tendon withdrawn with mild traction	3+

A short experiment of a series of five animals was carried out with this idea in mind. These results are tabulated in Table II. It can be seen that excellent results followed secondary wrappings done on tendons whose primary repair had been immobilized for thirty five days or longer long enough for differentiation of the structures to occur. In these tendons it was easy to free the adhesions. In tendons immobilized less than thirty five days the dissection was far more difficult because of lack of differentiation between tendon and adhesion. The secondary wrapping of tendons is believed to be a promising procedure and should be investigated further. If the period of immobilization following primary suture is thirty five days or longer, tendons followed by polythene wrapping might prove to be extremely valuable in restoration of tendon function.

SUMMARY AND CONCLUSIONS

1. An experimental method for the investigation of primary tendon repair within the flexor tunnel, in the dog, is presented.
2. The use of absorbable and nonabsorbable tubes to block the cross growth of adhesions from tendon to extratendon tissues has been investigated.
3. Tubes made of thin polythene film were found to be most suitable for this purpose because they are flexible and cause no tissue reaction.
4. Tendons heal strongly within polythene tubes if immobilized forty days or longer.
5. Tendons blocked away from the extratendon tissues by polythene tubes following primary suture within the flexor tunnels and immobilized forty days or longer approach normal function while control tendons approach nonfunction.

REFERENCES

1. J. B. Lippincott Company
J. B. L. 212 1941
Australia 23-1000
) Surgery of Modern Warfare
Writ Surg, Gynec & Obst 75
2. Posch, J. I. Primary Tendon Repair & Clin North America 28 1323 1949
3. Koch, S. L. Division of the Flexor Tendons Within the Digital Sheath Surg Gynec & Obst 78 929 1944
4. Mason, M. L. The Treatment of Open Wounds of the Hand & Clin North America 28 426 1949
5. Construction of the Digital Tendon Sheath J Bone & Joint
the Flexor Tendons of the Hand J Bone & Joint
Experimental Study Upon the Prevention of Adhesions
Ann Surg 87, 885 1937
as a Permanent Tendon Sheath J Bone & Joint
Tubes in Tendon Suture Insect 1 69 (1949)
A. Coulson C. and Hopwood, M. B. Use of
Quaternary Ammonium Compound for the Surgical Seal Ann J Surg 77 43 1949
6. Brown, M. H., Grindler, J. B., and Crank, W. McK. Preliminary Report on Experimental and Clinical Studies With Polythene Film Proc Staff Meet May, Clin 22 403 406 1947
7. Mason, M. I. and Allen, H. S. The Fate of Healing of Tendons Ann Surg 113 494 459, 1941

HEMIPPELVECTOMY

MARK M. RAWITCH, M.D., BALTIMORE, MD

(From the Department of Surgery The Johns Hopkins Hospital and University)

THE hindquarter amputation is frequently considered so mutilating a procedure and of such forbidding magnitude as to be properly excluded from the category of acceptable surgical operations. While it cannot be denied that the resultant deformity is extremely grave it must be remembered that it is inflicted as the result of a procedure offering the only hope of cure in many otherwise inoperable neoplasms of the upper thigh and pelvic girdle. Moreover, in the present state of operative technique and fluid replacement therapy it is a procedure well within the capabilities of any competent surgeon. Relatively few such operations are recorded despite a number of publications showing the progressive decrease in mortality. Gordon Taylor¹ has performed 21 hindquarter amputations with 6 deaths. The last 3 patients, all of whom recovered, were operated upon subsequent to his Presidential Address on Amputation.¹ This is still the largest single reported series of such procedures. As recently as 1942 Morton's³ report of 4 cases with no operative mortality was outstanding. The older reports of a mortality of 75 per cent and 50 per cent have been replaced by more recent reports of as many as 8 successive operations without mortality.⁶ The reports of Leighton² in 1942, of Sugarbaker⁵ in 1943, and of Pack^{4, 6} in 1946 and 1947 are among the most helpful to the surgeon planning to perform a hemipelvectomy. The present report is aimed at a clear presentation of the technical features of the operation. We wish to emphasize the essential straightforwardness of this surgical procedure rather than to present any new method for its performance. Two of the patients are of unusual interest, one in whom amputation was performed for a Marjolin's ulcer and another a 12 day old infant with extensive and deforming lymphangiomas and hemangiomas of the limb and pelvic girdle.

The term hemipelvectomy is simpler and more readily understood than the more complicated terms applied to this procedure. Malignant tumors of the upper thigh which invade the pelvis or the muscles attached to the pelvis are probably more safely removed by hemipelvectomy than by hip joint disarticulation. A moment's reflection will show that from the standpoint of numbers of structures and muscle masses to be divided the hemipelvectomy is a simpler procedure than the hip joint disarticulation. Anteriorly in the hemipelvectomy the only muscle divided is the psoas. Posteriorly the quadratus piriformis and the gluteus maximus at its origin are the only muscles to be divided, aside from the levator ani and ischioavernosus. The final wound is certainly easier to close than the wound left by a hip joint disarticulation. From the standpoint of functional disability there is little to choose between the two operations since a prosthesis is not likely to be worn after either procedure. A few descriptions of such prostheses may be found⁷

Hemipelvectomy has been performed for every variety of malignant tumor. It seems probable that the greatest success will be achieved with such slow growing lesions as chondrosarcoma and liposarcoma, which form extensive local tumors but metastasize late so that a sufficiently radical procedure may effect a cure. The squamous cell carcinoma (Marjolin's ulcer) of the first patient is an unusual lesion to require this operation.

TECHNIQUE

The type of anesthetic agent is immaterial both general and spinal anesthesias having been used. The choice here has been pentothal anesthesia with nitrous oxide supplement. The bladder is emptied and the catheter left as a guide to the urethra. The lower abdomen is included in the field. Medially the towels are clipped to the side of the genitals in front, and alongside the anus behind. With the extremity draped free, the opposite side of the sacrum and the shoulder of the same side are elevated on sandbags to permit easier manipulation of the limb. The hip and thigh on the operative side are thus lifted off the table facilitating the posterior phase of the procedure.

Anteriorly the incision extends from the symphysis to the anterosuperior spine and then for several inches along the iliac crest. The lateral insertion of the inguinal ligament is detached from the anterosuperior spine and its medial portion is separated from the pubis together with the rectus and pyramidalis insertions after the fascial attachments to the iliopectineal fascia are divided. The deep epigastric vessels thus exposed are ligated and divided. Blunt dissection then strips away the peritoneum and exposes the iliac fossa widely (Fig. 1). One can easily see the external and internal iliac vessels, the ureter and bladder and the rectum behind the peritoneum. The external iliac vessels have been ligated in this series since some reports have remarked upon the risk of the central portion of the posterior flap, if the common iliac vessels are divided. Pick³ advocated ligation of the common iliac artery for greater comfort in the posterior dissection and suggested prophylaxis of the slough in the posterior flap by a V shaped excision of the central portion. The psoas muscle is divided at a convenient level. There is no notable bleeding. The femoral nerve thus exposed is ligated and divided. This completes the anterior dissection except for the symphysis pubis. By dissection with fingers and periosteal elevator the symphysis is exposed. A curved clamp is forced through the space between the urogenital diaphragm and the symphysis to grasp a Gigli saw by which the symphysis is divided. In either case the large plexus of veins behind the pubis may cause troublesome bleeding which is controlled temporarily by packing. The division of the psoas muscle with the femoral nerve, the external iliac vessels and the symphysis constitutes the anterior phase of the operation.

The incision is not continued posteriorly. The tendency is to fashion too generous a flap posteriorly and while time will be saved by fashioning a short posterior flap, the danger of closure under tension must be kept in mind. From the posterosuperior iliac spine the incision sweeps down around the buttock, well above the trochanter and passes around to meet the an

terior incision two or three inches from the midline. The short posterior skin flap is elevated and the origins of the gluteus maximus divided. There appears to be no virtue in preserving the gluteus maximus. This muscle is lifted forward, the patient's hip is flexed and adducted, and the piriformis muscle is exposed with the superior and inferior gluteal vessels at its upper and

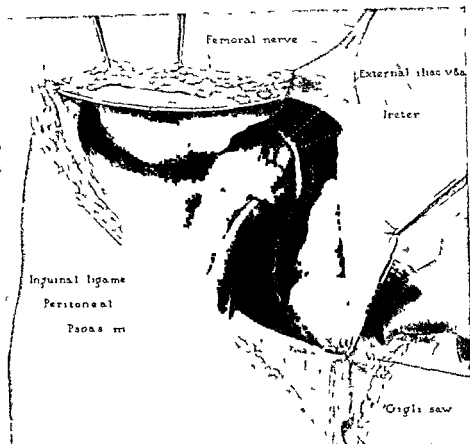


FIG 1.—The inguinal ligament has been divided, revealing the contents of the inguinal canal. In the male the

lower borders respectively (Fig 2). These vessels are secured and the piriformis muscle is transected, exposing the sciatic nerve which is ligated and divided. The tough sacrospinous and sacrotuberous ligaments are divided. One need only divide the quadratus lumborum muscle close to the ilium to complete the posterior dissection. A Gigli saw can now be passed around the sacroiliac joint which is cut through (Fig 3). If the tumor has not invaded the bony pelvis there is no harm in leaving a fragment of ilium attached to the sacrum. It will now be found that the hindquarter is attached only by

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the levator ani and ischioavernosus muscles. The levator ani muscle is cut through and the ischioavernosus muscle is clamped, divided, and transfixed. With the specimen removed, bleeding from the retropubic veins can be readily controlled by mattress sutures over strips of gelatin sponge. The relative simplicity of the procedure despite its magnitude is apparent. The bony pelvic ring has been divided in two places. Three muscles of significance—

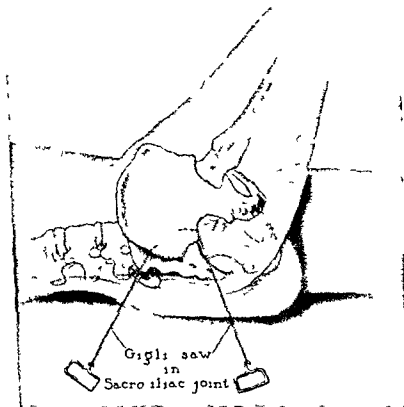


Fig. 3—All the soft tissue posteriorly have been divided and a Gigli saw is sawed through the pelvis around the sacroiliac joint which is cut through. When this has been done the limb will remain attached only by the ischioavernosus and a few fibers of the levator ani.

the psoas, quadratus lumborum, and piriformis—have been divided through their bellies. The gluteus maximus has been divided at its origin. The iliac and gluteal vessels and the femoral and sciatic nerves complete the short list of important structures divided. The levator ani and ischioavernosus muscles are taken almost in passing and disengagement of the attachments of the inguinal ligament anteriorly and of the sacrospinous and sacrotuberous ligaments posteriorly are simple and bloodless maneuvers.

Eight days later hemipelvectomy was performed. It was rendered difficult by the patient's severe skeletal deformities. Thus the anterior surface of the lumbar vertebral bodies pressed against the right iliac crest. The operation required 3½ hours, during which time the patient received five pints of blood and 250 c.c. of plasma without any change in general condition. Because all the skin of the buttock and the right scrotum with its contents had to be removed, an anterior skin flap was fashioned. The posterior incision actually crossed the midline skirting the anus.



Fig. 4 (Case 1)—H. M. (J.H.H. 1005). Squamous carcinoma (Marjolin's ulcer) in numerous sinus tracts penetrating deeply through right buttock. A recent attempt at direct excision was balked by the extent of the tumor into the pelvis. The right heel bent out of the way for this photograph, ordinarily rested against the area of the ulcer.

Pathologic Report—On the buttock and upper thigh was a large excavated ulcer 20 cm. in diameter. The surrounding skin was rolled and hypertrophied and sinus tracts led from the ulcer through the fascia and muscle. The base of the ulcer was thick, indurated and heavily scarred. The ulcer base extended toward the symphysis and down to the obturator foramen, both sides of which were covered by dense indurated scar. Microscopic examination of the ulcer showed a well-differentiated squamous cell carcinoma. There were no metastases in the lymph nodes.

In the anterior dissection it is important to open the iliac fossa widely, while in the posterior portion one must carefully reflect the gluteus maximus muscle to expose the gluteal vessels which are then readily ligated.

COMPLICATIONS

The urethra was injured in one patient (Case I) in whom the nature of the primary disease required sacrifice of the right half of the scrotum and its contents. Primary repair was unsuccessful and healing was delayed. In one patient the vagina was incised. The wound was repaired and healed per primam.

Hernias have not been reported after this operation and skin closure is all that is required. Because the peritoneum and its contained bowel tend to fall over the sharp edge of the transected sacrum we have tacked the lateral edge of Poupart's ligament to the anterior edge of the cut surface of the sacrum protecting the peritoneum and the bowel from possible injury. A drain is laid in place at either end of the incision the subcutaneous tissues are approximated with silk and the skin is closed with silk sutures.

Shock has not been a problem. Transfusions were given to all patients from the start of the operation. Distention did not occur. The second and third patients were out of bed on crutches the day after operation and left the hospital on the twenty first and sixteenth day, respectively their wounds having healed per primam. The first patient had a preliminary colostomy with consequent prolongation of his convalescence. The two men patients had temporary loss of sexual powers. Anemia has not been observed as a postoperative phenomenon.

CASE REPORTS

CASE 1 (173000)—H. M. was a white man, aged 40 years. This remarkable man had a congenital or neonatal paraplegia with an extreme flexion deformity. He had spent most of his life sitting on the shrunken deformed lower extremities. At the age of 10 years he developed an ulcer of the right buttock which was excised as a 'trophic sore'. In retrospect it seems more likely to have been an ulcerated bursa due to pressure by the right heel on the left as a result of the deformity which doubled the legs beneath him. Despite

right buttock was invaded by a solid tumor growing into the pelvis. A complete excision was abandoned. Fig. 4 shows the condition after this operation. Pathologic study revealed the tumor to be a squamous cell carcinoma. This was then a Marjolin's ulcer developing in thirty year old sinus tracts which had presumably resulted from incision of an adventitious bursa.

Hemipelvectomy seemed the only feasible operative approach complicated by the large area of skin involved, closely approaching the anus, and invading half of the scrotum. Pathologic examination showed no pelvic metastases. There had been lifelong urinary frequency and difficulty in control. In view of the proximity of the sinus tracts to the anus and of the possibility that the rectum might have to be sacrificed, a sigmoid colostomy was performed on Feb. 8, 1940 after exploration of the pelvis and abdomen showed no metastases.

The postoperative course was marked by a slowly developing hematoma and a separation of a portion of the wound. A small urethral fistula developed through the wound, entailing long use of a retention catheter. This was complicated in turn by the development of a vesical calculus which required a suprapubic cystostomy. However, he made a complete recovery from this series of difficulties and finally the colostomy was closed (Fig 5). Sphincter control was normal. He gained over thirty pounds in weight and returned to full employment. It took a considerable period of time before he felt comfortable in sitting. Sexual power was temporarily lost but eventually returned. Two and one half years after operation he shows no metastases and is in good health.

Summary—A 40 year old man with a congenital paraplegia developed a Marjolin's ulcer with carcinomatous invasion of the buttock and pelvis. Hemipelvectomy was performed after preliminary colostomy. Partial wound separation, a urethral fistula, and a vesical calculus complicated recovery. He is well two and one half years after operation.



7



8

Fig 7 (Case 1)—J. T. (JHH 44545). Osteogenic sarcoma of upper femur. A. There is a biopsy incision. Note the swelling reaches to groin. B. Roentgenograms show extensive bone formation and the high level of the tumor.

CASE 2 (448040)—J. T. was a 50 year old white woman. Eight months before admission the patient noticed discomfort in the right thigh. After one month severe nocturnal aching pain made its appearance and she noted swelling of the thigh. The swelling increased progressively and finally two weeks before admission she gave up working. In the last two or three weeks she had become alarmed and worried and had lost about ten pounds in weight. There were no other symptoms.

Physical examination was negative except for the right thigh. The upper third was involved in a large firm poorly outlined swelling beginning just below the inguinal ligament



Fig 5 (Case 1)—Jan 7 1947 eleven months after amputation. The right scrotum and its contents were removed at the original amputation. Note the use made of the remainder of the scrotum in closing the wound. The dressing on the left covers the incision left after closure of the colostomy a few days before this photograph was made.



Fig 6 (Case 1)—Post operative roentgenogram. The atrophic of muc and hemiproliferation and the distorted spine are due to the congenital deformity.

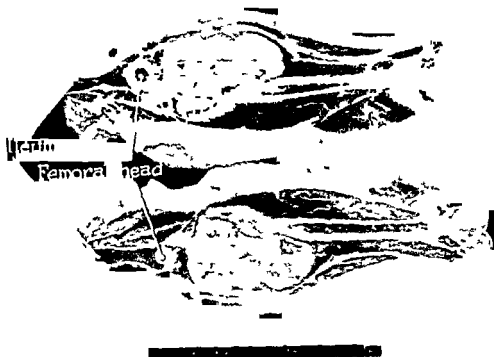
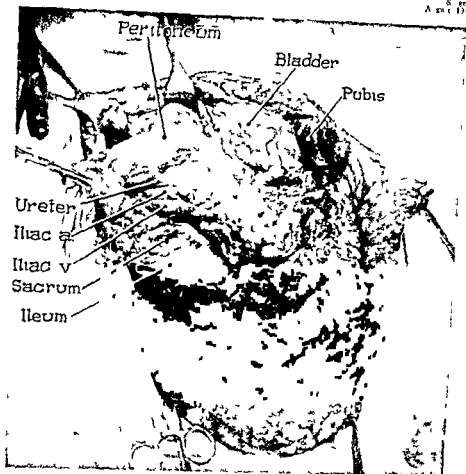


Fig. 9 (Case 1)—Specimen II (left). Note what scant margin would have been afforded by a hip joint disarticulation.



Fig. 10 (Case 1)—Left peroperative roentgenogram. In this instance a fragment of ilium and a fragment of pubis remain. If the tumor involved the femur this the specimen would have been completely resected.



A



E

Fig. 8 (Case 1) — A. Wound just before closure begun. The saw has cut through the acetabulum joint at an angle leaving a fragment of ilium posterior to it. The stump of the iliac vessels are plainly seen. The lateral portion of the inguinal ligament will be sutured to the anterior edge of the sacrum in order to protect the peritoneal sac from the sharp edge of the acetabulum of wound at time of closure.

sections showed a sarcoma with numerous areas of bone formation from spindle cells of varying size and shape. There appeared to be a good deal of tumor cartilage as well as bone. The impression was osteogenic sarcoma.

On Jan. 26, 1948, forty-eight hours after operation, the patient was out of bed and learning to use crutches for the first time. The catheter was removed on the third day. Voiding was satisfactory. Distention did not appear. The wound healed per primam, and by the tenth day she was up and about most of the day (Fig. 11, A and P). Three weeks after operation she walked out of the hospital to her car to begin a 1800 mile trip as a passenger.

She did well at home until she was abruptly taken severely ill on April 1, 1948. She developed deep jaundice, became comatose, and died on April 10, 1948. No autopsy was obtained. It seems highly probable that she died of homologous serum hepatitis developed as a sequel to the blood transfusions received during operation.

Summary—A 50 year old housewife was subjected to hemiplectomy for an osteogenic sarcoma of the upper thigh which had caused symptoms for eight months. She was ambulant on the second day. The wound healed per primam and recovery was rapid. She died, apparently of homologous serum jaundice three months after operation.



Fig. 1* (Case 3)—O. P. M. (J. H. H. 4770). Osteogenic sarcoma. Preoperative appearance showing the great soft tissue swelling reaching the groin although the primary osteous involvement (Fig. 11, A) is much lower.

CASE 3 (42,066)—O. P. M. was a 30 year old Negro man. He was first seen in June 1941 complaining of pain and swelling in the lower right thigh of nine months duration.

A biopsy was performed at another hospital in February 1941 and reported to show callus. In March 1941 he had fallen injuring the swollen area. The swelling and pain increased. Roentgen films in June 1941 showed an area of destruction on the anterior and lateral aspect of the lower third of the femur with bone proliferation about the femur. The lesion was suspected of being a sarcoma but a chronic non suppurative osteomyelitis seemed a reasonable possibility. In July 1941, the femur was explored. The cortex was hard, the medullary cavity was small and at the distal end of the femur was what appeared to be a large soft callus. Microscopic study showed bone formation from osteoid tissue and it was felt that this represented callus and neither tumor nor infection. The wound healed well and he was discharged diagnosed as having chronic sclerosing osteomyelitis. The callus was presumed to be the result of the previous biopsy.

In October 1941 at another hospital the tumor was excised so much of the thickness of the femur being resected that in December 1941, an iliac bone graft was performed. He remained in that hospital until March 1942 when he returned to the Johns Hopkins Hospital.

and fixed to the deep tissues (Fig 7, A). Roentgenograms (Fig 7, B) showed almost complete destruction of the upper third of the femur by a large tumor mass in which there were many areas of calcification or bone formation well out in the soft tissues. Biopsy of the tumor showed a sarcoma which varied from area to area, in some places appearing like a fibrosarcoma, in others forming bone and tumor cartilage of a kind not appearing extremely malignant, although this was obviously not a pure chondrosarcoma. There were no demonstrable pulmonary or bony metastases. It appeared improbable that a hip-joint disarticulation would remove the tumor with any margin of safety and hemipelvectomy was decided upon.

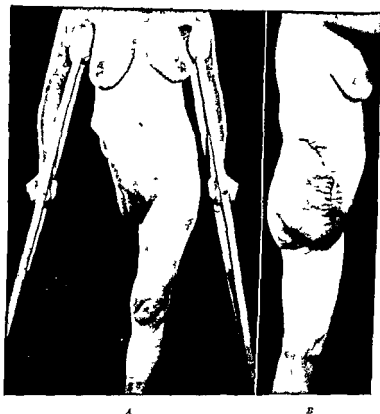


Fig 11 A and B (Case 2)—Photographs taken fourteen days after operation

On Jan 24 1948 a right hemipelvectomy was performed in the manner described (Fig 8 A and B). There was no intrapelvic extension of the tumor. The sacroiliac joint was cut through irregularly as seen in the roentgenograms (Fig 10), and the pubis was cut through just to the right of the symphysis. The right side of the vagina was opened and repaired with fine catgut and silk in several layers. The operation required three hours during which time the patient received a continuous transfusion of five pints of citrated blood. Her condition was good throughout. The short posterior flap was adequate for closure and a Penrose drain was left in either end of the wound. A retention catheter was left in the bladder. Hemoglobin after operation was 13 Gm and five days later 12.5 Gm.

Pathologic Report—There was a large well encapsulated tumor 14½ cm. in diameter in the upper third of the thigh arising from the femur (Fig 9). It was made up of a gelatinous rather firm, grayish white material containing some cystlike areas. The microscopic

sections showed a sarcoma with numerous areas of bone formation from spindle cells of varying size and shape. There appeared to be a good deal of tumor cartilage as well as bone. The impression was of osteogenic sarcoma.

On Jan. 26, 1948, forty-eight hours after operation the patient was out of bed and learning to use crutches for the first time. The catheter was removed on the third day. Voiding was satisfactory. Distention did not appear. The wound healed per primam, and by the tenth day he was up and about most of the day (Fig. 11, A and B). Three weeks after operation he walked out of the hospital to her car to begin a 1,800 mile trip as a passenger.

She did well at home until she was abruptly taken severely ill on April 1, 1948. She developed deep jaundice, became comatose, and died on April 10, 1948. No autopsy was obtained. It seems highly probable that she died of homologous serum hepatitis developed as a sequel to the blood transfusions received during operation.

Summary—A 50-year-old housewife was subjected to hemiplectomy for an osteogenic sarcoma of the upper thigh which had caused symptoms for eight months. She was ambulant on the second day. The wound healed per primam and recovery was rapid. She died, apparently of homologous serum jaundice three months after operation.

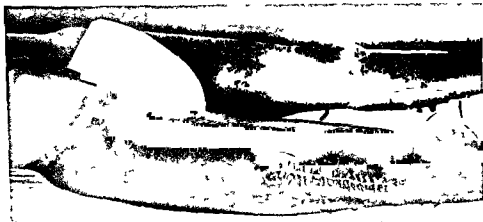


Fig. 12 (Case 3)—O. P. M. (J. H. H. 4700). Osteogenic sarcoma. Preoperative appearance showing the great soft tissue swelling reaching the groin although the primary osseous involvement (Fig. 14, A) is much lower.

CASE 3 (42,063)—O. P. M. was a 30-year-old Negro man. He was first seen in June 1947 complaining of pain and swelling in the lower right thigh of nine months' duration.

A biopsy was performed at another hospital in February, 1947, and reported to show 'callus'. In March, 1947, he had fallen injuring the swollen area. The swelling and pain increased. Roentgen films in June 1947, showed an area of destruction on the anterior and lateral aspect of the lower third of the femur with bone proliferation about the femur. The lesion was suspected of being a sarcoma, but a chronic non-union of a fracture with osteomyelitis seemed

more likely. The patient was hard to handle and it was decided to amputate the thigh and to remove the tumor. The wound healed well and he was discharged diagnosed as having chronic sclerosing osteomyelitis. The callus was presumed to be the result of the previous biopsy.

In October 1947, at another hospital the tumor was excised. So much of the thickness of the femur being resected that in December, 1947, an iliac bone graft was performed. He remained in that hospital until March 1948, when he returned to the Johns Hopkins Hospital.



Fig. 13 (Case 3) — *A* Preoperative roentgenogram. Note the extent of the tumor and the peculiar globular tumor masses. *B* Postoperative roentgenogram.



Fig. 14 (Case 3) — Frontal section of the lower portion of the spine showing the complete destruction of the bony structure and the peculiar globular metastases in the bony structure by soft tissues.

General physical examination was negative except for the right lower extremity. There was a great swelling of the right thigh level and fixed to the hip, which was adherent from the knee to the upper thigh (Fig. 12). The swelling surrounded the limb and the thigh from knee to groin, was very swollen and extremely tender. There was marked limitation of motion of the knee. Radiographic examination showed an extensive destructive process involving the entire distal half of the right femur (Fig. 13-1). This lesion had destroyed most of the cortex of the bone and extended out into the soft tissue. The femoral shaft in its midportion was uninvolved; a large mass with a calcified rim. There were numerous subcutaneous discrete nodular calcified nodules in the soft tissue. There was no evidence of distant metastasis. The long history suggests a sarcoma developing in a benign lesion probably chronic osteomyelitis.



FIG. 1. A and B (Case 3).—Photographs taken in the outpatient department three weeks after operation.

A biopsy on April 1, 1949, showed a friable gray cartilaginous tumor containing pieces of bone. Microscopic section showed a very cellular tumor composed of spindle cells with large hyperchromatic nuclei. The tumor cells appeared to be forming cartilage tissue in some areas and bone in others. The tumor was considered to be an osteogenic sarcoma.

The diagnosis of sarcoma being established, a hemipelvectomy was decided upon because of the extensive involvement of the soft tissues. No amputation was feasible at a level permitting the use of a prosthesis. Even a disarticulation of the hip would have meant transecting muscles and fascial planes only a few inches above the tumor.

On April 6, 1948 a right hemipelvectomy was performed. The operation took two hours and was well tolerated. He received 2,000 cc of blood during the procedure.

Pathologic Report—There were numerous enlarged inguinal nodes which did not contain tumor. There was a long scar extending 18 cm up from the knee with at least one palpable nodule, 0.5 cm in diameter in the scar. This nodule was a discrete encapsulated sphere of tumor. Twenty-two centimeters above the knee a cross section showed no gross tumor, but tremendous edema of muscles and subcutaneous tissue. Just distal to this was the main tumor mass which seemed encapsulated except anteriorly the capsule being a thin shell of bone. A remarkable feature was the presence of several round tumor nodules 1 to 4 cm in diameter in the soft tissue anterior to the principal tumor (Fig 14). The sections of the skin showed tumor nodules in the corium. In general, the tumor was an osteogenic sarcoma, as seen in the biopsy sections.

On the day following the operation he was up on crutches and his general condition was good. The wound healed per primam and he left the hospital on April 22, sixteen days after operation (Fig 15). Hemoglobin was 17.0 Gm before operation, 10.5 Gm the day after operation, and 9.8 Gm one week later.

Summary—A 30-year-old Negro man developed osteogenic sarcoma in the femur after several previous biopsies and roentgenograms had shown what appeared to be a benign lesion. This may represent sarcoma developing in Carré's chronic osteomyelitis. He was out of bed on crutches the day after hemipelvectomy and the wound healed per primam. He left the hospital on the sixteenth day after operation. He is well five months later except for diminution in sexual power.

Case 4 (16434)—T. J. was a 12-day-old white male. He was born with an extraordinary lymphangioma and hemangioma deforming the entire left lower extremity and invading the pelvis and buttock. A hemipelvectomy was successfully performed and is being reported in detail elsewhere.

SUMMARY

1 Hemipelvectomy is the only effective means of removing malignant tumors of the pelvic girdle and offers a wider margin of safety in the amputation treatment of malignant tumors high in the thigh.

2 The operative technique is described. The operation is not unduly complicated and the present day mortality is low.

3 Four patients, 12 days to 50 years in age are reported. Two operations were performed for osteogenic sarcoma and one each for Marjolin's ulcer and for extensive congenital angiomata.

REFERENCES

- 1 Gordon Taylor, G. Presidential Address on Amputation. *Tr. M. Soc. London* (1940) 1943: 83, 143, 161, 1943.
- 2 Leigh, J. *Ann. Surg.* 45: 913, 1941.
- 3 L. Merz, *Chirurgische Operations-Methoden*, 115.
- 4 Morton, H. *Surg.* 64: 1949.
- 5 Pack, G. T. and Ehrlich, H. E. Sacroiliac Disarticulation (Hemipelvectomy), *Ann. Surg.* 124: 611, 1946.
- 6 Pack, G. T. Ehrlich, H. E. *Ann. Surg.* 124: 611, 1946.
- 7 Sugarbaker, E. I. *Malignant Tumors of the Soft Tissues*, 81, 305, 1945.

SULFAMETHAZINE IN THE TREATMENT OF URINARY INFECTIONS DUE TO GRAM NEGATIVE BACILLI

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THE antibiotics in common use often fail to exert a sufficient therapeutic effect in urinary infections due to gram negative bacilli particularly in the case of *Bacillus proteus* and *Pseudomonas pyocyaneus*. Such failure is due to primary or acquired bacterial resistance^{1, 2} or less often to toxic reaction to the drug. In this report we are presenting clinical evidence that sulfamethazine is in certain circumstances superior to other chemotherapeutic agents for the treatment of urinary infection due to gram negative bacilli.

Our attention was drawn to sulfamethazine (2 sulfanilamido-4,6 dimethyl pyrimidine or dimethyl sulfadiazine) by reports of its high chemotherapeutic potency in vitro, and in vivo in laboratory animals against gram negative organisms.^{3, 4} Clinical trials with this drug (hereafter referred to as SMT) have been limited primarily to the treatment of coccal infections such as lobar pneumonia, pneumococcal meningitis and gonorrhea.⁵⁻¹⁴ The therapeutic results in over 500 patients of whom close to 400 had lobar pneumonia were very satisfactory and compared favorably with results achieved with sulfadiazine and sulfamerazine.

Sulfamethazine given orally in its free form is absorbed rapidly from the alimentary tract. The maximum concentration in the blood is attained within two to four hours^{15, 16} but there is considerable variability in the blood concentration from patient to patient with the same doses.^{7, 10, 21, 26, 27} It is, therefore, important to determine blood concentrations during the course of treatment and adjust dosage accordingly. In any given patient on divided daily dosage however blood levels can be maintained fairly constant.

The rate of excretion is approximately the same as that of sulfadiazine (SD)^{11, 18} and 40 to 80 per cent of the drug appears in the urine as the acetyl derivative.^{11, 15, 16} SMT and acetyl SMT are four to five times more soluble than SD and its conjugated form in urine at pH 5.5. Alkalinization of the urine increases the solubility of SMT an additional threefold and of its acetyl derivative 3.5 fold.^{18, 19} Since the renal toxicity of a sulfonamide is said to be directly related to its solubility in the urine,¹⁹ SMT may be expected to have the least renal toxicity of all the sulfonamides so far investigated. In experiments with mice, dogs and monkeys no renal complications were encountered^{19, 22} after prolonged administration of large doses of SMT daily. In man the incidence of toxic reactions during sulfamethazine therapy was approximately 5 per cent. These consisted of rash, vomiting and transient leuco-

TABLE I

CASE NO.	INITIAL DIAGNOSIS	ORGANISMS PRESENT BEFORE TREATMENT	ORGANISMS PRESENT AFTER TREATMENT	CLINICAL RESULT	SULFA METHA ZINE		(SMT) BLOOD LEVEL	I II III F S O N S F			REMARKS
					DOSE	DAYS					
1	Cystitis acute	F ch coli	None	Excellent	4 g	1	11	x			
2	Cystitis acute	F ch coli	None	Excellent	6	5	14.4	x			
3	Cystitis prostatic	F ch coli	F ch coli	Good	6	9	6.12.2	x			No tubercle bacilli found in urine
4	Cystitis acute with secondary ureters	F ch coli	None	Excellent	4	10	-	x			
5	Cystitis prostatic	F ch coli	None	Excellent	4	5	±	x			QMT blood concentration too low to be measured
6	Cystitis prostatic	A aerogenes	A aerogenes	Improved	6	13	5.6	x			
7	Cystitis prostatic	A aerogenes	A aerogenes	Improved	6	6	7.3.10.2	x			
8	Cystitis acute	B proteus	None	Excellent	4	4	4.5	x			
9	Bacterial prostatitis	F ch coli B proteus	F ch coli (little)	Excellent	4	8	5.0	x			Streptomycin prior to QMT toxic reaction
10	Cystitis prostatic	B proteus	F ch coli B proteus	Improved	6	28	1.1.1	x			
11	Bacterial prostatitis	A aerogenes	A aerogenes	Excellent	4	26	2.0	x			SD ST organism resistant to both drugs
12	Bacterial prostatitis	B proteus	B proteus	Excellent	6	4	7.0	x			SD ST, Streptomyces organisms resistant to both drugs

13	Recurrent pyritic abscess following peritonsillar abscess	Escherichia coli B 12	B 12	B 12	B 12	Excellent	6	11	11.0	x	S/D ST toxic reactions
14	Cystitis following prostatic abscess	Escherichia coli B 12	B 12	B 12	B 12	Excellent	6	13.0	13.0	x	Transient leukocytosis
15	Recurrent pyritic abscess following peritonsillar abscess	Escherichia coli B 12	B 12	B 12	B 12	Excellent	6	9	0.3	x	S/D ST organisms resistant
16	Cystitis following prostatic abscess	Escherichia coli B 12	B 12	B 12	B 12	Excellent	6	11	1.7	x	S/D ST toxic reactions
17	Intermittent pyritic abscess following prostatic abscess	Escherichia coli B 12	B 12	B 12	B 12	Excellent	6	7	1.6	x	S/D ST organisms resistant
18	Cystitis following prostatic abscess	Escherichia coli B 12	B 12	B 12	B 12	Excellent	6	7	1.1	x	S/D ST organisms resistant
19	Cystitis following prostatic abscess	Escherichia coli B 12	B 12	B 12	B 12	Excellent	6	13	2.4	x	S/D ST organisms resistant
20	Cystitis following prostatic abscess	Escherichia coli B 12	B 12	B 12	B 12	Excellent	6	11	1.1	x	S/D ST organisms resistant
21	Recurrent pyritic abscess following peritonsillar abscess	Escherichia coli B 12	B 12	B 12	B 12	Excellent	6	14	2	x	S/D ST organisms resistant
22	Cystitis following prostatic abscess	Escherichia coli B 12	B 12	B 12	B 12	Excellent	6	5	0.3	x	S/D ST organisms resistant
23	Cystitis following prostatic abscess	Escherichia coli B 12	B 12	B 12	B 12	Excellent	6	31	1.1	x	S/D ST organisms resistant
24	Cystitis following prostatic abscess	Escherichia coli B 12	B 12	B 12	B 12	Excellent	6	8	2	x	S/D ST organisms resistant

The cells of Staph aureus found only in the urine specimen

penia^{6,14} No serious reactions were encountered and there were no instances of renal damage. Only two patients were reported to have crystalluria, one of them also had hematuria.¹¹

This report deals with the results of sulfamethazine therapy in twenty four unselected patients with a variety of urinary tract infections (Table I). All patients had pyuria and positive urine cultures. Frequency, dysuria, fever, and leucocytosis were among the most frequently noted clinical symptoms and signs. Eleven patients had prior treatment with other sulfonamides and either failed to respond or had toxic reactions. Sixteen patients received penicillin and five streptomycin in adequate dosage without a therapeutic effect before sulfamethazine was given. Sixteen patients were either on constant drainage or were subjected to repeated catheterization for urinary retention. Obstructive pathology in the urinary tract, if present, was treated during SMT therapy.

Four to six grams of SMT were given in divided doses together with 2 to 2½ liters of fluid daily. NaHCO₃, 15 to 20 Gm., was also given daily in order to shift the urinary pH as far as possible toward the alkaline side. Even with this dose of alkali the pH ranged between 6 and 7.5. Most of the patients were treated for five to fifteen days (Table I). The duration of treatment was based upon the clinical and bacteriologic response.

The urine specimens for culture were obtained by catheterization in all females and in most males. In a few instances a 'clean voided' specimen was obtained in male patients. Cultures were taken at intervals ranging from one to three days and were repeated about once a week after termination of treatment. Thereafter follow up studies were carried out on the patients for periods ranging from two to ten weeks. In planting the urine cultures the same sized loop was used in all cases. One loop was streaked over the surface of blood agar agar and endo plates. The plates were observed for forty eight hours.

While the patients were on SMT medication the urine was frequently examined for blood pus and sulfamethazine crystals. The pH was determined daily.

RESULTS

The results were evaluated on a clinical and bacteriologic basis and are summarized in Table I. The clinical response is indicated by excellent, if all symptoms disappeared; by improved if most but not all clinical complaints disappeared; and by poor if there was no clinical improvement. Bacteriologically the results are classified by the following types of response:

I Sterile urine

II In cases with mixed infection of the several bacterial strains present some were completely removed while the count of the remainder was markedly reduced.

III No change in the bacteriologic findings

Of twenty four patients who received sulfamethazine nine had Response I, ten had Response II, and five patients had Response III. The types of response under each primary diagnosis are summarized in Table II.

TABLE II RESULTS OF SULFAMETHAZINE TREATMENT IN RELATION TO DIAGNOSIS

PRIMARY DIAGNOSIS	TOTAL CASES	RESPONSE			TOTAL FAVORABLE RESPONSES
		I	II	III	
Benign prostatic hypertrophy, suprapubic prostatectomy	5	1	4	0	5
Cystitis, secondary to operation	9	3	3	3	6
Cystitis secondary to urethral stricture	2	0	2	0	2
Acute cystitis	3	3	0	0	3
Chronic hemorrhagic cystitis	1	0	0	1	0
Chronic cystitis secondary to prostatectomy	2	1	1	0	2
Urinary tract tuberculosis with secondary infection	1	1	0	0	1
Intermittent intractable cystitis, bilateral nephrostomy	1	0	0	1	0
Total	24	9	10	5	19

See text.

In patients with a II or III response the persisting organisms were tested for in vitro sensitivity to SMT and were found to be resistant. The same bacteria were also found to be resistant to SD and sulfathiazole (ST). Occasionally strains of organisms resistant to SD and ST were sensitive to SMT. The effects of treatment on the individual bacterial strains are summarized in Table III.

TABLE III RESULTS OF SULFAMETHAZINE TREATMENT ON INDIVIDUAL ORGANISMS

UNIVALENT INFECTIONS			
BACTERIA	TOTAL NUMBER OF CASES	NUMBER OF CASES CLEARED	NUMBER OF CASES NOT CLEARED
<i>Esch. coli</i>	5	4	1
<i>A. aerogenes</i>	2	0	2
<i>B. proteus</i>	1	1	0
MIXED INFECTIONS			
BACTERIA	TOTAL NUMBER OF CASES	CASES IN WHICH BACTERIA WERE REMOVED	CASES IN WHICH BACTERIA WERE NOT REMOVED
<i>Esch. coli</i>	10	4	6
<i>A. aerogenes</i>	10	9	1
<i>B. pyocyaneus</i>	12	5	7
<i>B. proteus</i>	5	4	1
<i>Staph. aureus</i>	2	2	0
Hemolytic tr	1	1	0
<i>Str. viridans</i>	1	0	1
Nonhemolytic str	2	1	1
<i>Str. faecalis</i>	3	1	2
<i>Pneumococcus</i>	1	1	0

Of the eight cases with univalent infections there were three failures (two *Acrobacter aerogenes* and one *Escherichia coli*) due to bacterial resistance.

Of the sixteen patients with mixed infections two patients showed no bacteriologic response but one of them (Case 14) showed clinical improvement. Of the remaining fourteen patients four were cleared and ten showed definite bacteriologic improvement. In one of these patients (Case 18), with post-operative cystitis due to *Esch. coli* and *B. pyocyaneus*, *B. pyocyaneus* was cleared from the urine and *Esch. coli* decreased in number but there was no clinical response. This patient subsequently responded to streptomycin. The clinical results were satisfactory in the other thirteen patients.

Of ten strains of gram positive cocci (see Table I) found in nine cases of mixed infections six were removed from the urine in the course of SMT medication. Two strains of *Str. faecalis*, and two strains of nonhemolytic streptococci failed to respond to SMT. Some of these were removed by subsequent treatment with mandelamine. Of the gram negative bacteria 83 per cent of *B. proteus*, 75 per cent of *A. aerogenes*, 53 per cent of *Esch. coli*, and 42 per cent of *B. pyocaneus* were removed during SMT treatment. Clinically, 86 per cent of all patients treated showed definite improvement.

Two patients had toxic reactions. One patient (Case 14) developed a transient leucopenia. Failure to maintain fluid intake while on SMT medication resulted in a SMT blood level of 25.9 mg. per cent. Following withdrawal of the drug, and hydration, the concentration fell to 5.1 mg. in twenty-four hours and the white blood cell count returned to normal within forty-eight hours. Another (Case 16) developed an allergic skin rash following eleven days (66 gm.) of therapy. Withdrawal of the drug resulted in prompt recovery. This patient was also a bacteriologic failure. The responsible organisms were resistant to SMT, SD and ST but were subsequently cleared by an intensive course of streptomycin.

DISCUSSION

Analysis of our results shows that 37.5 per cent of the patients treated were cured and 41.5 per cent were improved both clinically and bacteriologically indicating a satisfactory response to medication in 79 per cent of the patients. Thirteen patients had no prior medication with other antibiotics; of these forty-six per cent were cured and 31 per cent improved. It is notable that of eleven patients in whom previous treatment with sulfadiazine and sulfathiazole had failed, nine (82 per cent) showed a favorable response to sulfamethazine. Two other patients who had an unsatisfactory result with streptomycin responded favorably to sulfamethazine. These findings also compare favorably with the results reported from the use of other chemotherapeutic agents for similar infections.^{2, 20, 31}

The results of streptomycin therapy in urinary infections due to gram negative organisms, exclusive of infections in paraplegic patients are variable, ranging from 10 to 90 per cent of the patients treated. The results are limited by the toxicity of bacteriologic reactions which have been reported, the expense and inconvenience of administration and financial considerations are further disadvantages of streptomycin therapy.

Sulfadiazine therapy has been widely applied and has been beneficial in 57 to 74 per cent of the patients treated.^{26, 27, 28} Patients with a single bacterial organism in the urine responded better than those with mixed infections. In the patients treated with SMT there was an equally favorable response in both types of infection.

Sulfathiazole has been efficacious in 65 per cent of patients with urinary infections.^{29, 32, 30} N-445 (3,4-dimethyl-5-sulfanilamido-isoxazole) desirable in

cause of its high degree of solubility and low toxicity was effective in 36 per cent of patients with infections caused by *B. proteus* and *Esch. coli*.¹¹ Sulfathiazine although reported to be highly effective (86 per cent) apparently is of value only against *Esch. coli*.¹²

SMT has a lower incidence of systemic toxicity and of renal toxicity than SD or ST. In the series of patients reported here no instances of crystalluria, hematuria, or azotemia developed as a sequel to its use.

In two patients in whom the blood concentration of SMT was in excess of 25 mg. per cent and urinary pH was acid, SMT crystals were not found in the urinary sediment.

SUMMARY

The results of treatment of twenty-four patients with urinary tract infections caused by gram-negative bacilli are described. Of the patients treated 79 per cent showed a favorable response.

The clinical and bacteriologic results observed with SMT compare well with the most favorable results obtained with other drugs. The lack of renal toxicity and the low incidence of systemic reactions are notable. Furthermore, SMT has been used successfully in some cases in which SD and ST and streptomycin had failed or where treatment had to be discontinued because of toxic reactions. Penicillin, as is well known, has no effect on gram-negative bacilli.

In two of the failures the organisms found to be resistant to SMT responded subsequently to streptomycin and in another to mandelamine (*Str. faecalis*). In vitro sensitivity tests were used as a basis for the choice of the most suitable drug.

CONCLUSION

Sulfamethazine is a valuable addition to the list of chemotherapeutic agents for urinary infections due to gram-negative organisms because of its extremely low renal toxicity and its effectiveness not only when used as the initial drug in the treatment but also after others have failed to control the infection.

REFERENCES

1. Finland M, Murray R, Harris H, W. Kilham L and Merd M. Development of Streptomycin Resistance During Treatment. *J. A. M. A.* 132: 1621, 1946.
2. Pool T I and Cook, L. A. *Practical Concepts of Treatment of Infections of the Urinary Tract*. *J. A. M. A.* 133: 584, 587, 1947.
3. Schweinfurth F P and Letwin I J. Sulfamethazine In Vitro Action on Enteric Pathogens as Compared With Sulfadiazine and sulfamerazine. *J. Bact.* 49: 193, 197, 1946.
4. Schmitt L H, Scler C L and Hughes H B. The Chemotherapeutic Activities of Sulfamerazine and Sulfamethazine. *J. Pharmacol. & Exper. Therap.* 81: 43, 57, 1944.
5. Loughlin F H, Bennett R H and Langman M E. Treatment of Pneumococcal Pneumonia With Sulfamethazine. *Ann. Med.* 29: 568, 573, 1944.
6. Meyer A. Sulfamethazine in the Treatment of Urinary Infections. *Ann. Med.* 29: 568, 573, 1944.
7. Miltz A. Comparison With Sulfathiazine.
8. Takematsu W and J. Pneumococcal Meningitis—Recovery With Sulfamethazine. *Lancet* 1: 649, 1943.

The results of treatment with this drug in twenty patients in this hospital were much better than in our results with sulfathiazine. (To be published.)

- 9 Johnson A G Sulphamezathine in Gonorrhea in the Male, Brit J Ven Dis 20
31 33, 1944
- 10 Dowling H F New Chemotherapeutic Agents in Treatment of Infectious Diseases
—Sulfamerazine and Sulfamethazine M Ann District of Columbia 12 469 471,
1943
- 11 McDermott W, Gilligan D R Wheeler C and Plummer A Clinical Studies of
Sulfamethazine New York State J Med 44 394 397 1944
- 12 Jennings P A and Patterson W H Sulphamethazine—Clinical Trial in Children,
Lancet 2 303 309 1942
- 13 251 1948
- 21 Ferguson C and Hershey, T H Streptomycin in Genitourinary Infections J Urol
57 932 937 1947
- 22 Adcock J D and Plumb R T Streptomycin for Urinary Tract Infections J A
M A 133 510 584 1947
- 23 Pulaski E J Streptomycin in Surgical Infections, Infections of the Genito Urinary
Tract Ann Surg 124 392 401 1946
- 24 Bandler C G Roen P R and Molaine V J Streptomycin in Genito Urinary In
fections J Urol 59 90 110 1948
- 25 Garvey F H and Canning T E Streptomycin in Urinary Infections, J Urol 60
176 186 1948
- 26 LaTowsky L W The Clinical Use of Sulfadiazine in Non-specific Urinary Tract
Infections Use of Sulfadiazine in
lactic to Prevent Post
thiazole Sulfacetamide
tion Proc Staff Meet
tions J Urol 44 116
- 27 Sattl
- 28 H. L. thiazole Sulfacetamide
tion Proc Staff Meet
- 29 Culp 124 140
1940
- 30 Alvea F P Sulfathiazole Therapy in Urinary Tract Infections J Urol 47 919
2 3 1942
- 31 Naras J The Treatment of B With a New Sulfonamide (N
With sulfathalidone (Ibthalylo
- 32 Everett H S Vosberg G A and With sulfathalidone (Ibthalylo

MECONIUM PERITONITIS

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MECONIUM peritonitis is a sterile reaction in the peritoneum of the newborn infant resulting from the escape of intestinal content. It is an uncommon condition which is not too well understood and which is believed to result from a number of different causes. Most reports in the literature are those of autopsies and the number of proved cases with patients surviving is small. We wish to report one patient with meconium peritonitis with an associated atresia of the terminal ileum who was operated upon and survived.

In 1838 Simpson¹ published his observations on this condition with a review of the literature comprising 25 cases. Rudnew,² in 1915, reported a series of 40 cases. According to Abt³ 60 additional cases were reported up to 1924. In all a few more than 100 cases have been reported to date.

Meconium peritonitis of the newborn infant is a pathologic entity completely different from acute bacterial peritonitis. It is an aseptic chemical peritonitis caused by the entrance of meconium into the peritoneal cavity through a perforation of the intestinal tract. This peritonitis occurs during intrauterine life, at the time of birth or immediately after birth. The perforation is thought to occur some time after the fourth or fifth month of fetal life. Meconium is a sterile mixture of bile, cast off epithelial cells, swallowed liquor amni, pancreatic, gastric, and intestinal secretions. Peristalsis, which probably begins early in fetal life, would appear to be necessary to cause rupture of the intestine.

Analysis of the cases reported by Rudnew² shows that approximately 50 per cent are associated with demonstrable intestinal obstruction of one sort or another ranging from developmental intestinal atresia through common adult causes such as adhesions, volvulus and intussusception. In these cases the mechanism of meconium peritonitis is fairly clear. Meconium within the intestinal lumen is thought to stimulate peristalsis which when working against an obstruction causes a perforation of the bowel wall with extrusion of the meconium into the free peritoneal cavity. 'Meconium ileus' was thought by Landsteiner⁴ to be a frequent cause of perforation of the bowel. This disease is associated with fibrosis of the pancreas and absence or diminution of pancreatic secretion. Lacking this secretion the meconium within the bowel becomes puttylike and adherent to the bowel wall so that it cannot be propelled along the gastrointestinal tract. This may set up an obstruction to the lumen of the bowel and perforation may occur proximal to it.

Whatever the cause the perforation of the bowel usually closes prenatally and frequently the site of perforation is not found at operation or at autopsy.

The peritoneal reaction is that of a chemical or foreign body peritonitis with meconium deposits the formation of dense adhesions agglutination of loops of bowel and calcification.

Of the other 50 per cent of cases in which meconium peritonitis exists without demonstrable organic obstruction many causes have been listed. Trauma was considered of the utmost importance by Zillner.³ Ulcers of the bowel Meckel's diverticulum the appendix, and other congenital diverticula are the sites of perforation. Still other cases of meconium peritonitis have been described one by Boikan⁴ in which there is no satisfactory explanation for the perforation.

Many of these children are born dead or die soon after birth. Those who survive present a picture of intestinal obstruction.

In 1944 Neuhäuser⁷ reported three cases from the Children's Hospital in Boston in which it was possible to make the diagnosis preoperatively by means of x-ray examination. The diagnosis in the case to be reported was also made preoperatively by x-ray examination. In addition to the picture of intestinal obstruction, x-ray examination showed scattered calcifications in the peritoneal cavity. Litten⁸ felt that calcification may occur as early as twenty-four hours after the onset of the peritonitis. In neonatal intestinal obstruction the presence of shadows of calcium density in the abdomen should make the diagnosis frequently possible.

CASE REPORT

J. H. C., a 4-day-old white male weighing 7 pounds 13½ ounce, was admitted Feb. 17, 1948 with a diagnosis of intestinal obstruction. This was the first child of a 21-year-old primipara, term pregnancy and labor of two hours and the condition was said to be mild. The mother continued to vomit periodically until admission to this hospital. Vomitus was sometimes black and sometimes dark green. The mother noted one stool the character of which was not known. Several enemas were given but were ineffectual. The abdomen became increasingly distended and the child's condition deteriorated rapidly.

Physical examination on admission revealed an acutely ill child who was pale dusky and lethargic. The skin had lost its turgor, was dry and inelastic. Temperature was 101° F. by rectum, pulse 110, respirations 40. The heart sounds were poor but the lungs were clear. The abdomen was moderately distended, soft and doughy in consistency. In the right lower quadrant there was a soft indistinct mass approximately 3 cm. in diameter. On rectal examination was not done.

Hemoglobin of 14 Gm. a red blood count of 4,500,000 with a predominance of granulocytes. Carbon

Urinary was normal except for 20 red cells per high power field. No stool was obtained for examination.

An x-ray examination of the abdomen was made on admission and was reported as follows: Abdominal films showed gas in the stomach and small bowel loops in the left upper quadrant only. There were fluid levels in the upright position. Fine calcifications were scattered throughout the abdomen. There were a few linear deposits on the inner surface of both lateral abdominal walls. There was a collection of small densities in the left side of the pelvis and another large collection in the region of the cecum. Conclusions were intestinal obstruction proximal to the colon and meconium peritonitis. The latter is often associated with atresia of the ileum (Fig. 1).

Intravenous fluids were administered and a catheter was passed into the stomach and connected to a continuous suction apparatus. After seven hours of treatment the child's condition had improved considerably and operation was decided upon.

Under light drop ether anesthesia supplemental with continuous oxygen administered through a nasal tube a right rectus muscle splitting incision was made and the peritoneum exposed. It was markedly thickened and inflamed and within it areas of calcification were counted. The peritoneal cavity was entered with considerable difficulty because of agglutination of the bowel to the anterior peritoneum (Fig. 2). There appeared to be no free peritoneal space. Everywhere loops of small bowel were agglutinated to one another by vascular adhesions. Immediately beneath the incision there was a dilated loop of small



FIG. 1.—Preoperative x-ray view of the abdomen with the patient upright showing scattered calcium throughout the peritoneum, especially in the right lower quadrant. On this film the diagnosis of meconium peritonitis was made.

bowel approximately 9.5 cm in diameter and 5 or 6 cm in length. This loop was dissected out from other loops of more normal appearing bowel and was found to terminate in a blind pouch. Adjacent to this was found a small collapsed loop of small bowel approximately 8 mm in diameter which also ended in a blind loop. This segment of bowel was dissected out and found to enter the cecum approximately 7 cm distally. The cecum and a cecocolon were completely collapsed but appeared to have a lumen. Saline solution was injected into the collapsed terminal ileum until it and the cecum were distended with fluid. It then became apparent that a complete atresia of the terminal ileum existed. Because of the agglutination of the peritoneal contents it was impossible to determine whether this was the only point of atresia. The mesenteries of the two blind loops described were continuous

with each other. The proximal bowel was markedly thickened and friable, but its blood supply seemed adequate. During further freeing of the proximal dilated loop a traumatic perforation occurred at a point where a cordlike adhesion was attached. The bowel at this point was extremely thin, and it was thought that it was probably the point of prenatal perforation and the source of meconium peritonitis. The accidental opening was closed.

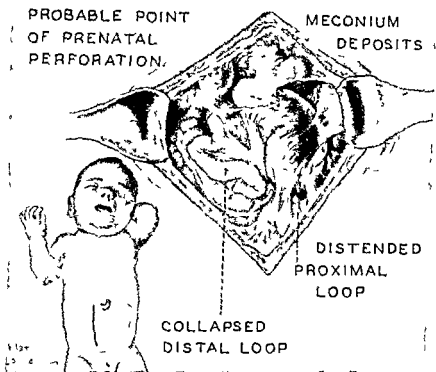


Fig 2—Artist's reconstruction of operative findings. Note the two blind ends with enormous distention of the proximal loop.

the wound was closed in layers. One hundred cc of 1% penicillin and 1/2 gm streptomycin in solution were placed in the peritoneal cavity in the region of the anastomosis before the peritoneum was closed. During the procedure the child was given two blood transfusions of 50 cc each. At the conclusion of the operation the child was extremely pale and cold and the extremities were blue. He was returned to the bassinets where warmth was applied, duodenal suction was continued and a slow drip of fluid was administered. He was put in an oxygen tent and given 10,000 units of penicillin and 25 mg of streptomycin intramuscularly every three hours.

Microscopic examination of the biopsies from the peritoneum showed granulation tissue with marked infiltration by inflammatory cells chiefly large mononuclear phagocytes lymph



Fig 3—Photomicrograph of biopsy from the peritoneum showing marked inflammatory reaction with crystalline deposit and calcium.

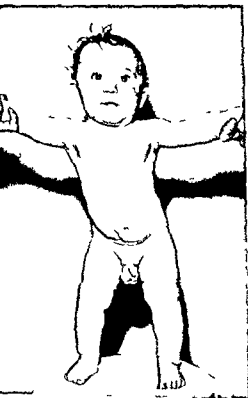


Fig 4



Fig 5

Fig 4—37-week patient at 37 weeks showing normal development and nutrition. The small right hydrocele is obvious.

Fig 5—Chest X-ray film of the abdomen at 37 weeks showing diminution in the degree of calcium deposit. Compare with Fig 3.

ocytes and plasma cells. In some areas there were collections of polymorphonuclear leukocytes. Scattered throughout there were extensive areas of fat necrosis and small areas of calcification (Fig. 3).

Postoperatively the child's condition improved steadily. He was given enemata several times each day to distend the colon and stimulate peristalsis. The abdomen became softer and flatter and peristaltic waves returned. The suction was discontinued on the third postoperative day, he was given glucose solution by mouth on the fourth postoperative day, and formula on the fifth postoperative day. From that time on he continued to maintain nutrition orally with an occasional supplement of subcutaneous fluid. Stools soon became normal in appearance and frequency. The postoperative course was complicated by a purulent otitis media and a superficial wound infection, both of which responded to treatment. He was discharged from the hospital on March 19, one month after admission.

The patient has been followed in the pediatrics outpatient department the last visit being Oct. 29, 1949, thirty-seven weeks after birth, and development has been progressive at a normal rate. Weight at 7 weeks was 9 pounds 7½ ounces and at 3½ weeks 20 pounds 12 ounces. Except for an occasional stuffy nose the patient has been entirely well. He has had no colic and no vomiting. The bowels have been regular. The diet which he takes well included at the time of his last visit fruits, vegetable, and Tabulum as well as a milk formula. Physical examination revealed a well developed and well nourished baby (Fig. 4) who appeared entirely normal. A right hydrocele previously noted was diminishing in size. One of us ever thought that a little thickening could be felt to the right of the scar in the position of the calcium deposits seen in an earlier x-ray view. It is interesting to note that the first x-ray film of the abdomen (Fig. 1) revealed marked diminution of the calcium in comparison with earlier films. The baby was to all intents and purposes completely well.

SUMMARY

A case of meconium peritonitis in a 4-day-old infant is reported. The diagnosis was made preoperatively on the x-ray appearance of the abdomen. A successful surgical procedure resulted in apparent complete cure at the age of 37 weeks. At this time the calcium deposits in the peritoneum were disappearing.

REFERENCES

1. Simpson, James Y. Peritonitis in the Fetus in Utero. *Edinburgh M. J.* 15: 390-414, 1939.
2. Pulawski, W. Ueber die spontanen Darmrupturen bei Foeten und Neugeborenen. *Basel* 1911; *Fachlehrbuch Kinderkrankheiten* 23, pp. 6.
3. Abt, I. A. Fetal Peritonitis. *M. Clin. North America* 15: 611-622, 1931.
4. Landteimer, K. Darmverschluss durch eingeklemmtes Meconium. *Frankfurter Centralblatt für allg. Path. u. path. Anat.* 16: 903, 1903.
5. Zillner, F. Ruptura flexurae sigmoideae inter partum. *Virchows Arch. f. path. Anat.* 96: 318, 1884.
6. Boikan, W. M. Meconium Peritonitis From Spontaneous Perforation of the Ileum in Utero. *Arch. Path.* 9: 1164-1165, 1930.
7. Neuhauer, F. B. D. Roentgen Diagnosis of Fetal Meconium Peritonitis. *Am. J. Roentgenol.* 51: 411-422, 1943.
8. Litten (cited by Runkewitz).

CLINICAL EXPERIENCES WITH THE ARTIFICIAL KIDNEY

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THE value of an artificial kidney in certain types of uremia was first demonstrated during 1948. Following the pioneer work of Kolff¹ in Holland and Murray² in Canada, other papers have appeared reporting the successful use of such an apparatus.

The principle of utilizing dialysis to clear the blood of waste products was introduced by Abel, Rowntree and Turner in 1913.³ The application of this principle to the human patient was made possible by the clinical development of heparin as a safe nontoxic anticoagulant. Various types of apparatus have been described, all of which are fundamentally similar. The machine used at the Royal Victoria Hospital is a Kolff artificial kidney with certain modifications. It consists essentially of a wooden drum around which 100 feet of cellophane tubing is wound in spiral fashion. This tubing has a flat diameter of one inch. The drum revolves at a constant speed of 25 revolutions per minute in a bath of the following composition:

NaCl	0.6%
KCl	0.04%
NaHCO ₃	0.2%
Glucose	2.0%
Tap water	100 liters

The bath is kept at a constant temperature of 100° F.

In setting up the apparatus the patient is heparinized and a glass cannula is inserted into the radial artery and connected to the cellophane tubing. After passing through the machine the blood is returned into the antecubital vein by a variable speed pump.

The patient's blood is thus exteriorized across a semipermeable membrane and the diffusible substances within the blood are brought into equilibrium with those in the bath water. By this means the excess nitrogenous waste products are removed from the circulation while the important electrolytes remain unchanged.

The chief value of such an apparatus is in the treatment of uremia due to reversible conditions of the kidney. A temporary clearing of the blood by dialysis may give the kidney time to recover from damage and resume function. In such cases the artificial kidney may be lifesaving. We have also found the machine useful in an occasional case with a permanent renal lesion. In many such patients there is sufficient kidney function to maintain life under ideal conditions. However, uremia may be precipitated by infection or other

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complications and the artificial kidney provides a means of helping such a patient over the crisis

The types of uremia in which dialysis is of value can be summarized as follows

- 1 Acute renal lesions with uremia
 - (a) Fulminating acute glomerulonephritis
 - (b) Acute poisoning—mercury phenol salicylates

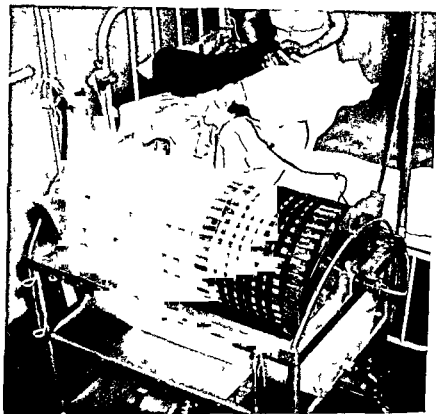


Fig 1—The artificial kidney in use

- 2 Lower nephron nephrosis type of lesion

Anuria following

 - (a) Incompatible transfusion
 - (b) Sulfonamide administration
 - (c) Crush syndrome
 - (d) Severe burns
 - (e) Eclampsia
- 3 Anuria following a prolonged period of hypotension

Postoperative anuria
- 4 Preparation of the uremic patient for a surgical procedure

- (a) Prostatic obstruction
- (b) Infections of the kidney

In the past seven months we have treated six patients with uremia with the artificial kidney. The purpose of this paper is to outline the effects of this dialysis on the uremic state and on the patient as a whole.

Effect on Blood Chemistry—It is obvious that the diffusible electrolytes in the blood will reach an equilibrium with those in the bath water. The cellophane tubing forms a semipermeable membrane which is impervious to larger molecules such as proteins.

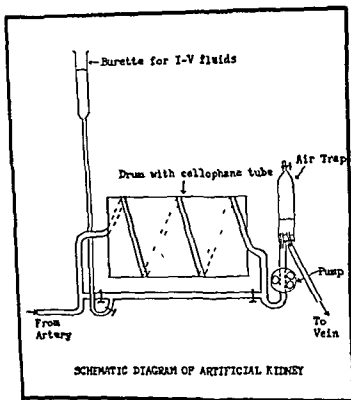


Fig. —Diagram of the mechanism of the artificial kidney

The nonprotein nitrogen of the blood drops at a rate of 10 to 30 mg per cent per hour while the bath water nonprotein nitrogen increases in proportion. The rate of diffusion slows as the dialysis progresses but we have never found it necessary to change the bath within an eight hour period.

In many cases the blood nonprotein nitrogen rises after the dialysis is stopped. This is because the excess nitrogenous wastes in the tissues are not discharged as quickly as they are removed from the blood by the kidney. This theoretically necessitates a longer period of dialysis but in practice we have found that an eight hour treatment is usually sufficient to clear the blood and improve the uremic condition.

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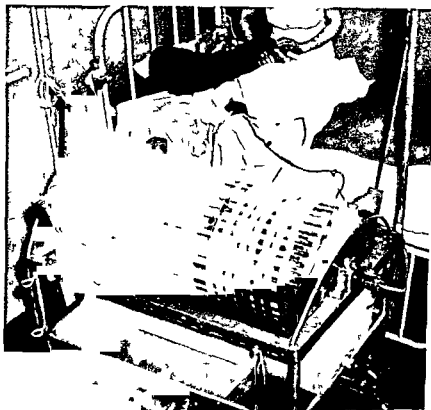


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Postoperative anuria
- 4 Preparation of the uremic patient for a surgical procedure

be important. The white cells decrease in number at the beginning of the dialysis but return to normal within a few hours. This is due to coating of the cellophane with leucocytes because of a positive chemotaxis.

Effect on the Patient—The process of dialysis with the artificial kidney is well tolerated even by the poor risk patient. The machine does constitute an arteriovenous shunt but the capacity of the shunt is only 200 cc. a minute and this is not enough to embarrass the circulation. The rapid return of blood into the right side of the heart may theoretically cause a rise in venous pressure and lead to pulmonary congestion. So far we have observed no harmful effects. In all cases the pulse and blood pressure have remained constant throughout and there has been no evidence of cardiac failure.

No other significant effects of dialysis have been noted except for an occasional patient who has felt subjectively improved after a period of treatment.

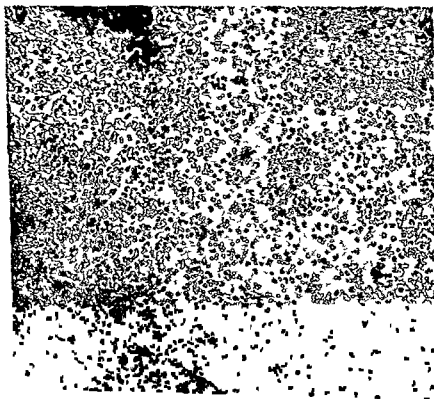


Fig. 4—Section of the cellophane tubing showing trapped leucocyte

CASE REPORTS

CASE 1—A man aged 40 years had uremia due to prostatic emphysema, bilateral arteriosclerosis and left lower lobe pneumonia.

Dialysis was carried out for three hours with a drop in the nitrogen nitrogen from 121.5 to 60.5 m. per cent.

The patient was in moribund condition and died a few hours after treatment was discontinued. Autopsy showed marked degenerative changes in the kidneys.

The bath water is low in calcium because with an open tank and low CO₂ pressure calcium salts tend to precipitate. The result is a gradual fall in blood calcium which can be prevented by giving the patient 10 Gm. of calcium gluconate intravenously every three hours.

If acidosis exists it may be aggravated by the dialysis. This tendency can be overcome by giving 500 cc. of 1/6 molar sodium lactate intravenously when ever the CO₂ combining power falls below 50.

The bath contains a high concentration of glucose to prevent hemolysis. This diffuses into the blood and causes a hyperglycemia which may reach a level of 500 to 600 mg. per cent. It is important to avoid this effect in diabetic patients. In any case the administration of insulin may be advisable.

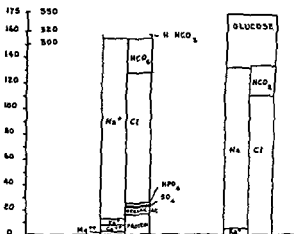


Fig. 3 - Comparison of the concentration of blood plasma to the dialysing fluid

Effect on Circulating Blood—One of the early problems encountered in this work was the determination of the optimum dosage of heparin. It soon became apparent that heparin was lost by dialysis and large amounts were required to prevent coagulation. If the blood clots within the kidney the treatment must be abandoned accordingly it is far better to use too much heparin than too little. An initial dose of 150 mg. is given to the patient intravenously and another 150 mg. is run through the kidney. Kolff has emphasized that metal connections must be avoided because they inactivate heparin. For this reason we have used glass cannulas and connections. During the course of the dialysis 50 mg. of heparin is added to the circuit every 1½ hours. This routine has worked very well and we have had no trouble with clotting since its adoption. Blood heparin levels show an adequate concentration at all times. At the end of the treatment the heparin is neutralized by giving 10 cc. of a 1 per cent solution of protamine sulfate intravenously.

The changes in the formed elements of the blood have been studied by DeLeeuw and Blaustein. They demonstrated a considerable degree of hemolysis in vitro which was due to the centrifugal effect of the drum and the mechanical action of the pump. In clinical cases this hemolytic effect does not appear to

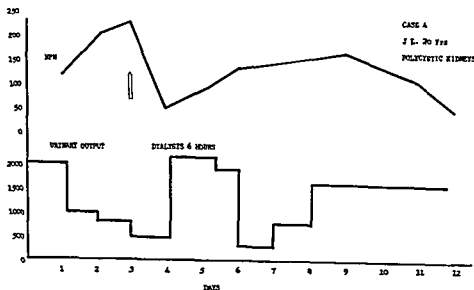


Fig 8—Chart of treatment in Case 4

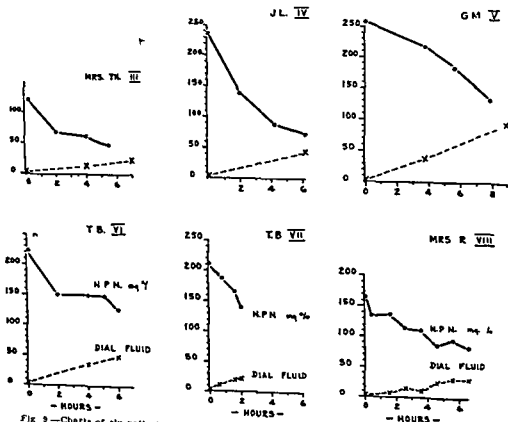


Fig 9—Charts of six patients treated with the artificial kidney, showing the fall in nonprotein nitrogen in the patient's blood and the corresponding rise in the bath water

CASE 2—A man aged 33 years had anuria due to nembutal poisoning. Dialysis was carried out for one hour, during which time the nonprotein nitrogen dropped from 130 to 13.5 mg per cent. Treatment was stopped because of clotting in the tubing. The patient continued to improve and the nonprotein nitrogen dropped to normal in forty-eight hours and the urinary output increased. The good result in this case can hardly be attributed to the artificial kidney.

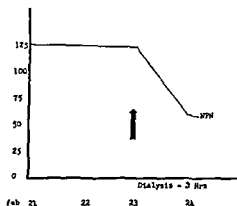


Fig. 5—Chart of treatment in Case 1

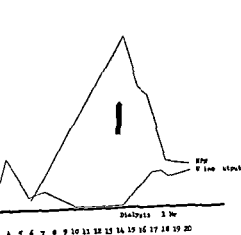


Fig. 6—Chart of treatment in Case 5

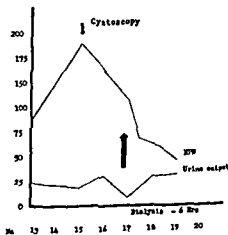


Fig. 7—Chart of treatment in Case 6

CASE 6—A woman aged 53 years had anuria due to bilateral ureteral obstruction by secondary carcinoma. A six-hour dialysis caused a fall in nonprotein nitrogen from 102 to 48 mg per cent with marked subjective improvement. She remained well for several weeks but the nonprotein nitrogen gradually rose and she died with uremia. Autopsy showed marked bilateral hydronephrosis and renal atrophy.

Case Reports

GIANT PHARYNGOESOPHAGEAL DIVERTICULUM

CASE REPORT

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FREQUENT reference has been made in recent literature to the problems met with in the treatment of pharyngo-esophageal diverticula. Lacey (1940, 1946), Harrington (1944) and Shallow (1948) have discussed the subject thoroughly in the presentations of their respective groups of cases while McNeely (1947), King (1947) and Sweet (1947) in their reports have also given information of great value in the management of these lesions. The present communication affords a review of our experience with a pharyngo-esophageal diverticulum apparently of unequalled size.

CASE REPORT

H. I. (Hospital No. 340) a Negro butler 52 years old was admitted to the Medical Service of the Memorial Hospital on Sept. 10, 1947 because of weakness and dysphagia of about six month duration.

The symptom had begun with the regurgitation of a portion of each meal. Liquids were retained at first provided they were taken slowly though with each attempt to swallow gurgling sound were usually heard and associated with a transient sensation of pressure in the chest. No medical attention was requested until weakness was experienced approximately five months later. A physician then diagnosed that the patient at that time weighed 130 pounds. A fluoroscopic examination was performed and immediate hospitalization was advised. The proposal frightened the patient and he refused all further attention. Five weeks later swallowed liquid could no longer be retained and shortly afterward referral to the hospital was recommended and accepted.

Physical Examination.—At admission he was found to be a strikingly emaciated and emaciated patient who looked desperately ill. Temperature was 98.6 F., pulse 80, respiratory rate 20. Blood pressure 116/84, weight 94 pounds. Numerous hard nontender lymph nodes were palpable on each side of the neck. The trachea was in the midline and the thyroid gland was not abnormal. On the right the area of mediastinal dullness was extended to the mid clavicular line and over it the breath sounds were considerably diminished. The other findings which were noted were not thought to be abnormal.

Laboratory Studies.—The hemoglobin concentration was 13.5 Gm. The red and white cell counts were 4100,000 and 12,300 with a differential white count of 82 per cent neutrophils, 14 per cent lymphocytes and 4 per cent monocytes. Blood urea nitrogen 36 mg. per cent, plasma chlorides 4.5 mEq. per cent, plasma proteins 7.0 Gm. per cent. The urine was not found to be abnormal.

Bariumograms revealed an enlarged oval mass lying in the mediastinum and in the right upper chest (Fig. 1 and 2). Its superior and inferior poles were opposite the first and sixth thoracic vertebrae respectively. The lateral border of the mass was about 9 cm. from the midline of the chest encroaching on the pleural cavity and compressing the right lung while anteriorly the mass was almost centrally located with a maximum diameter of about 9 cm. A definite fluid level was apparent in its cavity. The lower margin of the

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CASE 4—A man aged 20 years had congenital polycystic kidneys with renal failure and uremia. His condition was moribund. Dialysis was carried out for six hours with a drop in the nonprotein nitrogen from 34 to 11 mg per cent and creatinine from 1.5 to 0.3 mg per cent. During the treatment 44.8 Gm of nonprotein nitrogen were removed from the blood.

The following day the nonprotein nitrogen rose to 115 mg per cent as further nitrogenous wastes were released from the tissue. After ten days the nonprotein nitrogen dropped to 60 mg per cent and has remained at that level for the past four months. He is clinically well at present and is working. In this case the use of the kidney was a life saving measure and despite a chronic renal lesion the patient has remained well for some time.

CASE 5—A man aged 27 years had chronic glomerulonephritis with uremia. A nine-hour dialysis caused the nonprotein nitrogen to drop from 208 to 113 mg per cent and the creatinine from 2.1 to 1.6 mg per cent (93.5 Gm nonprotein nitrogen removed). The patient was improved after treatment and felt subjectively better for seventy-two hours. He then began to go downhill and died twelve days later. At autopsy the kidneys showed far advanced disease.

CASE 6—A man aged 58 years had postoperative anuria with renal failure. A six-hour dialysis caused the nonprotein nitrogen to drop from 224 to 128 mg per cent (50 Gm nonprotein nitrogen removed). Hepatic level at the beginning of treatment was 40 gamma and during dialysis averaged 20 gamma. This indicates an adequate anticoagulant effect. The patient was subjectively improved the day following dialysis.

CONCLUSIONS

1. The artificial kidney is an efficient means of removing nitrogenous waste products from the blood in clinical cases of uremia.
2. Dialysis is well tolerated by the patient and does not produce any harmful effects.

REFERENCES

1. At 1. J. J. Rowntree, I. C. and Turner, R. B. *J. Pharmacol. & Exper. Therap.* 5: 5, 1911.
2. Alwall, N. *Acta med. Scandinav.* 127: 55, 1947.
3. Kolff, W. J. *New Ways of Treating Uremia*. London: J. & A. Churchill Ltd.
4. Maclean, I. T., Ripstein, C. B., Delleuw, A. K. M. and Miller, G. C. *Clinical Medicine* 58: 453, 1948.
5. Murray, C., Delorme, E. and Thomas, N. *Arch. Surg.* 55: 50, 1944.
6. Murray, C., Delorme, E. and Thomas, N. *J. A. M. A.* 137: 1584, 1948.

mass was diminished when a small amount of a diluted barium mixture had been swallowed (Fig. 3). With complete filling of the cavity no barium was seen to pass into the distal part of the esophagus and during forceful exhalations with the epiglottis closed no change was observed in the size or in the outline of the mass. It was also later noted that the mass did not collapse when its cavity had been carefully emptied by lavage.

Bears were also noticed in the apex of each lung and discrete calcified nodules were reported in the perihilar areas and in the peripheral fields. These findings were regarded as evidence of healed tuberculosis.

Preoperative Treatment—A regimen of parenteral feedings was immediately begun but within five days a weight loss of ten pounds had been recorded. Numerous attempts were made to pass a Levine tube into the stomach (Fig. 4). When these efforts were abandoned a surgical consultation was requested. An emergency jejunostomy was performed and within three weeks a weight gain of twenty six pounds was achieved. A microcystic arena which was discovered when the dehydration had been corrected responded to transfusions with three pints of fresh whole blood.

A cervical lymph node was excised and found to be tuberculous.

One month after hospitalization an esophageal operation was performed. The diverticulum was entered directly and its lower margin was encountered 24 cm. from the upper incisors. The orifice of the distal part of the esophagus was not seen. The diverticular walls were thought to be fibrotic and adherent to the surrounding tissue. There was no evidence of active inflammation or of neoplastic change.

Operative Treatment—A two stage operation of the type described by Lakey was therefore undertaken (by L. A. M.) in the treatment of this lesion. Satisfactory anesthesia was obtained with the administration of nitrous oxide, oxygen and ether through an intratracheal tube.

The first stage of the procedure was performed on Oct. 13, 1947, after the diverticulum had been emptied by lavage. An incision at the anterior edge of the right sternocleidomastoid muscle was extended from the sternum to the level of the hyoid bone and carried through the skin, platysma and deep fascial layers. The anterior belly of the omohyoid muscle was transected near the point of its attachment to the hyoid bone. The right superior and inferior thyroid veins were ligated and divided. Access to the diverticulum was provided through the space between the trunks of the right carotid sheath and the right lobe of the thyroid gland. The pretracheal fascia was incised and the right inferior thyroid artery was ligated and divided.

The mobilization of the diverticulum was very difficult because of the fibrotic extensive adhesion about its walls. Gentle friction with sponge forceps was found to be of no assistance in the development of a cleavage plane but eventually recourse to intermittent air injections through the lavaging tube was discovered to be helpful in this phase of the dissection. When the diverticulum had finally been delivered from its bed its point of origin was palpable as a rounded orifice 4 cm. in diameter which lay posteriorly in the midline and immediately below the inferior pharyngeal constrictor muscle.

The size of the remaining mediastinal defect could not be diminished by inflation of the lungs. The cavity was therefore packed with gauze which was inserted about a rubber catheter. The dissection was resumed until the submanubria of the neck had been exposed. The tip of the lavage tube was then guided into the distal part of the esophagus. The diverticulum was implanted in the wound in a position which assumed an obtuse angle at the junction of its neck with the esophagus. There was no resistant traction on the wall of this structure. Multiple purse string sutures were taken in the wall of the fundus of the diverticulum to reduce its bulk. The skin incision was then closed about the free end of the catheter. This entire operation was tolerated well and the patient was returned in excellent condition to his bed.

The postoperative course was uneventful. Ambulation was encouraged after full recovery from the anesthesia. The jejunostomy feedings were continued. The lavage tube was withdrawn on the second day and liquids were thereafter administered by mouth. A penicillin solution was injected into the catheter each day. The mediastinal pack was removed in seven days.

Fig 1

Fig 2



Fig 3

Fig 4

Fig 3: Anteroposterior view of the thorax on admission. The

Fig 4: Anteroposterior view of the thorax after a barium mixture
has been administered to the distal part of the esophagus.
The size of the diverticulum, obtained

Microscopic Examination—The specimen was lined with epithelium of the type which is normally encountered in the esophagus. The walls were found to be fibrotic and infiltrated with many groups of plasma cells. There was no evidence of malignant change. Diagnosis was pharyngoesophageal diverticulum.

COMMENT

Though pharyngoesophageal diverticula are not infrequently encountered, those of the proportions here described are apparently extremely rare. We have found no previous record of a larger diverticulum of this type, and we know of no reported instance where compression of the lung was a coexistent finding.

We believe that certain aspects of the treatment of the larger diverticula merit special emphasis. A preliminary jejunostomy may be a lifesaving procedure when dysphagia has led to marked nutritional deficiency. The value of this measure in the case reported here where a gain of twenty six pounds was recorded in a period of three weeks has seemed indisputable to us. Another point of great importance is the technique of dissection once a decision to excise the diverticulum has been made. An adequate exposure is a prime essential, and in our opinion a generous incision of the type we have described provides the only surgical approach which will suffice in this respect. Unusual care is required also in division of the adhesions between the diverticulum and the walls of the esophagus. A technique of intermittent air injection is applied to these lesions may be of value in the development of a satisfactory cleavage plane and thus in the avoidance of inadvertent injury to other mediastinal structures.

Our preference for the two stage operation in the treatment of a diverticulum of this size will not be debated here. The many fascial planes invaded in the course of the dissection undoubtedly increase the risk of complicating cellulitis or infection of the mediastinum. We believe that we were able to minimize these dangers in this case by waiting for the sealing of the opened planes before we finally completed the removal of the diverticulum.

SUMMARY

The occurrence of a giant pharyngoesophageal diverticulum is reported and an account is given of its successful surgical removal.

A technique of intermittent air injection is also suggested as a means of aiding in the dissection of the sac and use of the two stage operation is unreservedly endorsed in the operative treatment of the larger diverticula of this type.

REFERENCES

1. Harrington, S. W. Pulmon Diverticulum of the Hypopharynx at the Pharyngoesophageal Junction. *Surgey* 18: 66-81, 1943.
- King, R. T. *Ann. Surg.*
2. Lahey, F. H.
3. Lahey, F. H.
- Ann. Surg.
4. McNealy, P. *Surgey*
5. Shallow, T. A. and Clerk, L. H. On the Analysis of the One Stage Sacral Sweet, R. H. Pulmon Diverticuli the One Stage Operation. *Technique and Technique of*

The second stage of the procedure was performed on Oct. 23, 1947. The various structures in the wound had not been altered in appearance. Traction sutures were inserted in the walls of the hypopharynx and esophagus near the diverticular orifice. Mosquito clamps were placed upon the diverticular neck along the proposed line of amputation, and the tissues medial to the clamps were then divided. Immediate closure of the sectioned layers was made with interrupted mattress sutures of fine chrome catgut. This sequence of clamping, incision, and repair was continued until the diverticulum was excised and the esophageal orifice was closed in its longitudinal diameter. The suture line was reinforced with interrupted mattress sutures of fine chrome catgut placed in the muscle layers of the esophagus and hypopharynx. The residual mediastinal defect was packed with gauze. The patient tolerated the operation well.



Fig. 5—Roentgenographic appearance of the esophagus nine months after operation. There are no abnormalities of the pharynx or esophagus.

Early ambulation was again encouraged and the regimen of jejuno-stomy feedings was continued. The living tube was removed on the third postoperative day. The pack was gradually withdrawn from the mediastinal defect and finally discarded early in the second week. To expedite the closure of the small remaining defect the patient was instructed to make forceful exhalations with the epiglottis closed at frequent intervals each day. Within two weeks the defect was believed to have been closed but a low grade fever developed somewhat later was then thought to be indicative of a walled-off abscess in this site. The sinus tract was therefore opened and a small amount of seropurulent fluid was discharged. The temperature was normal the next day. Oral feeding was begun and on the thirty-third postoperative day the jejuno-stomy tube was taken out. Shortly afterward the patient was discharged able to enjoy an unrestricted diet and retain it normally.

The mediastinal defect was found to be filled in approximately three weeks later. Roentgenograms at four and nine months after operation showed no abnormalities of the pharynx, hypopharynx, or esophagus (Fig. 5). A steady weight gain has been noted since the time of operation and at the most recent visit, Sept. 2, 1949, a weight of 144 pounds was recorded.

function was adequate for pneumonectomy. Bronchoscopy and electrocardiograms were normal. The hemoglobin was 10.2 Gm per cent. Fetal heart sounds and fetal movements were present. Three days prior to operation the patient was placed on 25 mg. of stilbestrol three times daily and 10 mg. of progesterone twice daily. She received transfusions of 500 cc. of citrated blood daily for two days preceding the operation.

A left pneumonectomy was performed on Dec. 8, 1947 under cyclopropane endotracheal anesthesia. The patient was placed in the prone position with the left side of the body at the edge of the table. A posterolateral incision was made and the pleural space was entered through the sixth intercostal space. The mediastinal pleura was incised exposing the bronchus, which was cleared and divided with clamps. The pulmonary artery, superior pulmonary vein, and inferior pulmonary vein in the order named, were individually cleared doubly ligated, and transected and divided. The lung was then delivered by separation, a few adhesions to the mediastinal pleura. The bronchial stump was then closed by a proximal row of mattress silk sutures. The cuff of bronchial tissue in the clamp was excised and a distal row of end-over-end silk sutures completely closed the bronchus. The bronchial stump retracted from sight into the mediastinum. The diaphragm was paralyzed by resecting a segment of the phrenic nerve. The wound was closed in layers without drainage. At the completion of the operation the intrapleural pressure was reduced -12 to -6.

The patient's condition was good during the operative procedure which lasted three hours and twenty minutes. She received 1,300 cc. of blood and 1,300 cc. of other fluid during the operation.

The postoperative course was excellent. Fetal heart sounds and movements were constantly present. The mediastinum was maintained in as neutral a position as possible by repeated thoracenteses. Isoniazid 50,000 units every three hours which had been started three days before operation was continued for two weeks. Streptomycin was not administered because of its possible danger to the fetus. The stilbestrol and progesterone were continued for sixteen days postoperatively.

The pathologic report was as follows: Gross. The specimen consisted of a left lung. The lobes were distinct. The external surface was dull red in color and shaggy. There was decreased crepitus throughout. At the apex of the upper and of the lower lobe were palpable nodular masses. On section the nodules were found to be caseous and necrotic masses surrounded by milky caseous areas. Microscopic. Lung tissue had an exudative appearance in the alveoli and many areas of cavitation surrounded by epithelioid cells and many multinucleated giant cells.

After the immediate postoperative period (first two weeks) the course was uneventful except for the maintained rapid pulse 100/110. Fetal movements were present and quite active. The urine consistently showed 1 to 2 plus albumin. Frequent blood pressure readings were normal. There was no evidence of toxemia of pregnancy. The sputum was converted to negative immediately after the operation and has remained so.

On Feb. 5, 1948 the patient was again presented to the combined medical-surgical conference and here it was the consensus of opinion that inasmuch as it was not known how a patient would fare with a labor following pneumonectomy delivery by cesarean section would be the procedure of choice. However at 8 A.M. on Feb. 18, 1948 a premature labor started with rupturing of the membranes. The patient was transferred to the obstetrical division. The obstetrical consultants at this time were of the opinion that inasmuch as the labor was small delivery from below could be accomplished safely and easily. The second stage of labor started at 4 P.M. of this day and one-half hour later with the aid of outlet forceps a normal male infant weighing 3 pounds 1 ounce was delivered. The mother showed no untoward effect.

The day following the delivery the pulse rate was 94 the first time that it had been below 100 since her transfer to the thoracic surgical service. Her postpartum course was uneventful and after three weeks she was returned to the tuberculosis service for further central science. Fourteen months after the operation both mother and child were in excellent condition and the mother's sputum was still negative for acid fast bacilli.

PNEUMONECTOMY FOR PULMONARY TUBERCULOSIS IN A WOMAN SIX MONTHS PREGNANT FOLLOWED BY A NORMAL LIRTH

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PNEUMONECTOMY for unilateral caseous pneumonic tuberculosis which cannot be controlled by collapse measures has become an accepted procedure in the treatment of tuberculosis complicated by pregnancy, all cases are individualized although certain general standards are followed at the Metropolitan Hospital. If the caseous pneumonic disease is discovered after the first trimester of pregnancy, it is the policy not to be concerned with the pregnancy, but rather to use any measure which would control the disease in the mother. Thus all types of collapse therapy have been used in the past. We have now another procedure which when the proper indications exist can be added to the list namely pneumonectomy. This case is being reported because it illustrates the trend in the treatment of tuberculosis complicated by pregnancy, and also because no similar case can be found reported in the recent literature.

Patient A C a 29 year old Puerto Rican woman was admitted to the Tuberculosis Service on Oct 16 1947, with the diagnosis of pulmonary tuberculosis. She was well until one month prior to hospitalization when she noted the onset of a cough productive of greenish yellow sputum without blood weakness afternoon fever and night sweats. She was pregnant at this time and a chest x ray film revealed the pulmonary disease.

Physical examination revealed a well developed poorly nourished Puerto Rican woman looking chronically ill but in no acute distress. There was increased tactile fremitus and dullness over the left side of the chest. Posttubercular rales were heard over the left apex. The heart showed no enlargement murmurs, or arrhythmias. Abdominal examination revealed a gravid uterus.

The following menstrual history was obtained. Onset at 16 years of age. The periods were always regular 28 day cycle with a flow for three days. Her first child was born on Feb 27, 1947. Menstruation began again in April 1947. She had normal periods in May and June. The period in July was abnormal so that it only lasted for two days and the flow was potty. This was the last menstrual bleeding.

A chest x ray film on Oct 16 1947 revealed the right lung to be clear. The trachea heart, and mediastinum were shifted to the left. The left lung showed a marked peral thickening and homogeneous clouding throughout. In the left intraclavicular area numerous highlights suggestive of cavitation were noted. The sputum was positive for tubercle bacilli on direct smear Cuffey. A diagnosis of extensive caseous pneumonic disease with cavitation of the left lung was made.

Control of the disease by artificial pneumothorax was attempted. A left pneumothorax was successfully induced on Oct 21 1947. After two weeks it was noted that the pneumothorax had failed to influence the cavities. A further study showed the lung to be adherent to the posterior chest wall over a wide area in the region of the cavities.

At a surgical tuberculosis conference on Nov 26 1947 it was the consensus of opinion that the interruption of a five to six month pregnancy would be a hazardous procedure and to allow the patient to go on with the pregnancy with an uncontrolled disease would be inviting disaster. It was therefore decided to treat the tuberculosis and allow the pregnancy to continue. A pneumonectomy was advised. The preoperative pulse rate ranged between 100 and 110. The blood pressure was 100/80. Ventilatory tests showed that pulmonary

Pancreatic Resection—The resection of the involved part of the pancreas by removing the presumed source of the pain would seem to promise a cure. The head is the most frequently involved part of the gland and to remove it the duodenum must be excised also. With involvement of the entire gland resection of all of it except a strip in the curve of the duodenum allows the duodenum to be undisturbed, leaves some glandular tissue for internal and external secretion and would offer a reasonable prospect for the relief of pain. This was the procedure adopted in the case being reported.

Total Pancreatectomy—The complete removal of the source of the patient's pain is logical and has been successful in the hands of Whipple and others. It is a radical procedure and a formidable one involving besides the removal of the pancreas and the duodenum resection of the stomach and common bile duct and implantation of the duct into the jejunum with a gastroenterostomy. The patient is made diabetic and the operation must certainly carry a higher risk than the less radical procedures.

Ligation of the Pancreatic Ducts—The theoretical basis for the ligation of the pancreatic ducts is that if the excretory duct of a gland is ligated the secreting parenchyma will atrophy, swelling and distention will disappear and the gland will be converted to painless fibrotic tissue. The difficulty here lies in the fact that the stones have already blocked the ducts and the pancreas has been largely converted to fibrous tissue—the factors which seem to cause pain in this syndrome. The discrepancy perhaps may be due to incomplete blockage of the ducts by stones so that secretion is not completely suppressed. A successful case has been reported.³ However in that instance the ducts were not isolated and ligated but several mass sutures were apparently passed through the head of the pancreas and tied, the assumption being that the ducts were occluded by this maneuver. This would seem to be a rather unsatisfactory procedure. The isolation of the pancreatic ducts as they enter the duodenum in the living patient is difficult and somewhat hazardous. I believe there is little reason to recommend this operation at present.

Sympathectomy and Vagotomy—The predominant disabling feature of this disease is the pain for which the patient seeks relief and the various procedures outlined are directed toward that end. The cure of an extensively damaged pancreas is impossible in most cases. Regardless of the method of treatment employed we are treating the pain rather than the disease. By interrupting the pain carrying paths from the pancreas relief should be obtained. It is a rational procedure and has been reported as being successful.⁴

The following case is being reported because it has certain features of interest. The patient was young 26 years with extensive calculosis and fibrosis of the pancreas without diabetes. Bilateral sympathectomy and vagotomy the latter both subdiaphragmatic and supradiaphragmatic had been performed without permanent relief of pain. A subtotal resection of the pancreas gave relief from pain without causing diabetes or digestive disturbances.

CALCULOSIS AND FIBROSIS OF THE PANCREAS

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THE syndrome of pancreatic calculosis and fibrosis associated with intractable abdominal pain is apparently being recognized with increasing frequency. Over 200 cases of pancreatic lithiasis have been reported in the literature. The impetus that the work of Whipple and others has given to surgery of the pancreas and duodenum along with improvements in anesthesia and modern supportive treatment has encouraged surgeons to attempt more frequent radical surgical attacks on the pancreas. A good summary of the subject, with a bibliography is contained in a recent article by Ellison and Welt.¹

The object of this paper is to discuss briefly the surgical treatment of pancreatic calculosis and fibrosis and to report a case successfully treated by subtotal resection of the pancreas.

Undoubtedly many cases of pancreatic lithiasis occur without symptoms and it is seen occasionally as an incidental finding on a roentgenogram of the abdomen. Stones in the pancreas that are causing symptoms may be obscured however, by the barium in a gastrointestinal series so that a plain film should always be made.

The following methods of treatment have been recommended and used with reported success:

- 1 Pancreolithotomy
- 2 Pancreatic resection
- 3 Total pancreatectomy
- 4 Ligation of the pancreatic ducts
- 5 Sympathectomy and vagotomy

Pancreolithotomy—The most frequently used procedure has been pancreolithotomy. If there are only a few large calculi present in a localized area of the pancreas incision into the pancreas and ducts with removal of the stones would seem a logical procedure. However calculi can be and have been missed and left behind. A roentgenogram taken through the wound at the time of operation might be helpful in determining this point. It should also be remembered that the gland is a damaged one with fibrosis loss of parenchymal tissue and dilatation of ducts with ulceration and derangement of the ductal epithelium.

The fibrosis may play as large or a larger part in producing pain as did the stones. And finally the cause or causes that initiated the pathologic process may still be operating and the stones may re-form fibrosis may proceed and pain continue.

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The inulin test revealed free hydrochloric acid in the gastric secretion ranging from 2 to 18 clinical units. This would seem to indicate that despite two vagotomies vagal fibers to the stomach were still present. A glucose tolerance test gave successive values of 80, 120, 100 and 82 mg per 100 cc for blood sugar.

Castrote (inulin) roentgenograms showed a stomach that emptied slowly with some retention of barium after five hours, and a large antrum, duodenal bulb associated with a zone of narrowing in the upper portion of the second part of the duodenum at the level of the calcareous densities in the head of the pancreas. Some deformity of the first portion of the duodenum was present but there was no evidence of an active ulcer.

The patient was observed in the hospital for the next nineteen days. During this period he continued to complain of abdominal pain very severe at times, with vomiting.

It soon became apparent that the patient had a psychopathic personality. He was unreliable and at times surly and unkind to the nurses and other patients on the ward. As his history had indicated the psychologic background had been poor since childhood. He was examined by neurologic and psychiatric consultants and found to have no organic nervous disease but to have some psychopathic traits with inadequacy and to be a dependent type emotionally requiring an emotional crutch.

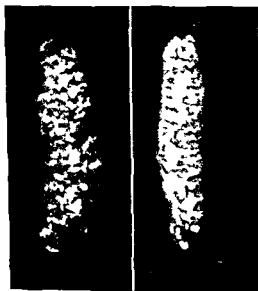


Fig 1 A and B—Roentgenogram of the pancreas after excision

It was felt that the patient needed psychiatric treatment. He had had three operations with transient relief from pain but the pain had always returned.

He continued to follow this advice and begged for surgery to relieve the pain. Since obvious organic disease was present which could be the cause of the symptom, it was decided to try to break the psychologic cycle by resecting the pancreas.

On March 24, 1948, he was operated upon. Anesthesia was induced with sodium pentothal followed by intratracheal cyclopropane, oxygen and helium with intravenous curare. The abdomen was opened through a transverse upper abdominal incision cutting across both rectus muscles.

CASE REPORT

C. J., a white man who worked as a stock clerk, 26 years of age was admitted to The Brooklyn Hospital on March 5, 1949. The chief complaints upon admission were a severe abdominal pain, nausea, and vomiting for several days.

The past history was interesting. He had been in good general health until five years before when he had had an attack of severe epigastric pain, nausea, vomiting, and weakness. He consulted a physician, who prescribed an ulcer diet which he followed irregularly.

He was married about that time and the history of the marriage becomes intermingled with that of the illness. Intermittent attacks of abdominal pain recurred over the next three years. During this period marital difficulties developed and he began to drink. Whatever the origin of the drinking may have been, as the attacks of pain became more severe he drank more and more to relieve the pain. At times the pain was so severe that either twenty-five glasses of beer or a quart of whisky was the only thing that gave relief. The pain was described as of severe agonizing boring quality extending through to the back and around the sides of the chest and leaving him weak and malnourished. It did not seem to be related to any type of food or to the time food was taken.

In 1946 the patient entered a hospital in New York. There a diagnosis of duodenal ulcer and "pancreatic tones" was made by roentgenogram. A right-sided thoracolumbar sympathectomy was performed. The patient left the hospital without having the left side operated upon for some reason but he experienced some relief of pain for several months. However the pain recurred the attacks became more frequent and during a severe attack he entered a hospital in Brooklyn about nine months before the present admission. While there, the abdomen was explored and the pancreas was found to be greatly enlarged, edematous and hyperemic. A diagnosis of acute pancreatitis was made and an infra-diaphragmatic vagotomy was performed. After this operation the pain was relieved for several months. Again the pain reappeared and became worse and about five months after the second operation the patient was admitted to another hospital in Brooklyn. There a left-sided transthoracic sympathectomy and supra-diaphragmatic vagotomy were performed. After this operation he was relieved of pain for about two months.

Seven days before the patient's admission to The Brooklyn Hospital he again began to have severe upper abdominal pain going through to the back. This was intermittent and at times agonizing in severity. Nausea and vomiting had occurred daily and he could retain only fluids. Four days before admission he passed several tarry stools but the stool was of normal color the following day. Appetite was very poor. There had been considerable loss of weight in the past few years from 160 to 135 pounds. He had recently noticed that the bowel movements had become more frequent, four to five a day and the stools were very loose.

Past history revealed that as a child the patient had been very close to his mother and feared and disliked his father. When he was 10 years old his mother died of heart disease and from that time until the age of 13 he suffered frequent epileptic seizures.

Physical examination upon admission revealed a 26-year-old man in acute distress, vomiting and complaining of upper abdominal pain. Color was good. The examination was negative except for the abdomen. It was soft and not distended. Tenderness without muscular pain was present in the epigastrium and the left lower quadrant. No masses could be felt. Right thoracolumbar, left thoracotomy and left upper recto-abdominal scars were present. Tenderness was present over the vertebral spines from the twelfth thoracic to the first lumbar.

A plain roentgenogram of the abdomen demonstrated a considerable number of irregular calcific densities extending throughout the abdominal cavity and tail of the pancreas.

Laboratory work-up showed a normal urinalysis and blood count. The Wassermann reaction was negative. The blood urea, the creatinin, the serum amylase and lipase were within normal limits. Fasting blood sugar was 90 mg per 100 cc. Blood cholesterol was 165 mg per 100 cc.

The operation time was five hour and fifty minutes. Whole blood totaling 1,000 cc. was given during the operation. The blood pressure during the procedure stayed at about 120 systolic and 80 diastolic. The pulse ranged between 80 and 100 and respirations 18 to 22 per minute.

Postoperatively the patient did exceptionally well. Temperature rose to 100.5 on the day of the operation and after that remained normal. There was practically no drainage through the catheter in the drainage tube which was kept under constant suction and the tube was removed in forty-eight hours. He was out of bed on the third day. Fluids by

Fig. 4



Fig. 5

Fig. 4—Diffuse fibrosis that has obliterated all the parenchyma except for a few islands of Langerhans.

Fig. 5—Cystic dilatation of ducts with some calcareous material still within the lumina.

A moderate number of adhesions were encountered, which were separated, and the pancreas was approached through the gastroduodenal omentum. It was found to be of about normal size, extremely fibrotic and densely adherent to the surrounding tissue. The gall bladder was thin walled, contained no stones, and emptied easily. No ulcer was palpated in the duodenum. Mobilization of the gland was begun by freeing the tail from the surrounding tissue and proceeding from the left to the right. Considerable force was required to insert a needle carrying a traction suture into the gland. Extremely dense fibrous tissue surrounded the gland, necessitating sharp dissection and it was necessary to clamp and ligate innumerable bleeding vessels including the splenic artery. The spleen was buried in adhesions and was not removed.



Fig. 1—Photograph of the gross specimen. On the right can be seen a dilated duct where the head of the pancreas had been coned out and cut across.

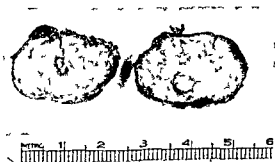


Fig. 2—Transverse section of the pancreas. The fibrotic character of the gland can be seen as well as a dilated duct containing stones.

The pancreas was resected by coning it out at the head to the right of the superior mesenteric vessels. Thus part of the head remained between the duodenum and the superior mesenteric vessels which were entirely uncovered when the pancreas was removed. It is believed that 85 to 90 per cent of the pancreas was excised.

The cut end of the jejunum was sutured over it. A large tube was brought out through the center of the wound. The wound was closed with cotton and wire sutures.

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The operative time was five hours and fifty minutes. Whole blood totaling 1,500 cc, was given during the operation. The blood pressure during the procedure stayed at about 120 systolic and 80 diastolic. The pulse ranged between 90 and 100, and respirations 18 to 20 per minute.

Postoperatively the patient did exceptionally well. Temperature rose to 100.5 F the day of the operation and after that remained normal. There was practically no drainage through the catheter in the drainage tube which was kept under constant suction and the tube was removed in forty-eight hours. He was out of bed on the third day. Fluids by

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Fig. 4—Diffuse fibrosis that has obliterated all the parenchyma except for the islets of Langerhans.

Fig. 5—Cystic dilatation of ducts with some calcareous material still within the lumina.

mouth were given as soon as he could take them. Soft diet on the fourth day, and full diet on the fifth day. Penicillin 50,000 units every three hours was given for six days. Parenteral fluids were given on the first, second, and third days. On the sixth day acetone appeared in the urine and the patient was given 1,000 cc of 5 per cent glucose in saline solution. After that, no further parenteral fluids were given.

No drainage appeared on the dressings after the drainage tube was removed and the wound healed by first intention.

Two days postoperatively the blood lipase was within normal limit. One week postoperatively the fasting blood sugar was 74 mg per 100 cc. A stool was reported as showing a moderate amount of undigested fat. Eight days after operation the glucose tolerance test was normal.

For the first few postoperative days the patient complained of severe burning pain at the site of the incision and deep in the abdomen. This gradually wore away and at the time of discharge on April 13, 1948, he had no complaint except occasional mild pain in the region of the right part of the transverse colon. Bowel movements were regular and the stools were of normal appearance.

Pathologic Report—

Gross. The specimen consisted of a partially resected pancreas, measuring 8 by 4 by 2 cm (Figs. 1, 2 and 3). The outer surface was well encapsulated and coarsely nodular. Only the main duct was definitely identified and it appeared dilated and filled with myriads of small hard white calculi which formed fairly large masses. On section the organ consisted of a relatively small amount of opaque firm, white to tan tissue arranged in lobules supported in a dense fibrous stroma. The accessory duct was filled with calculi. Small calculi were found embedded throughout the glandular substance, presumably lying in the duct system.

Microscopic. There was extensive fibrosis that divided the parenchyma into discrete rounded patches. There was a suggestion of regeneration of the parenchyma in the compact insular character of these patches. Islets of Langerhans were present in about normal numbers. The ducts many of which contained calculi were dilated and some organization of exudate had tended to incarcerate the stones and obliterate the lumina (Fig. 4 and 5).

Diagnosis.—Pancreatic calculosis with fibrosis was the diagnosis.

At the time of writing, seven months after the operation, the patient is feeling well. He has no pain, has a good appetite, and has gained seven pounds in weight since leaving the hospital. Stools are normal in appearance and a urinalysis on one occasion showed no glycosuria. He is such an unruly person that it is very difficult to keep in touch with him and have him return to the hospital for follow-up examination, which of course should be made frequently for the rest of his life.

SUMMARY

A discussion of the methods of surgical treatment of pancreatic calculosis and fibrosis is presented with a report of a case treated with apparent success by subtotal resection of the pancreas.

REFERENCES

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THE PHYSIOLOGIC BASIS OF OPERATIONS FOR DUODENAL, GASTRIC, AND GASTROJEJUNAL ULCER

A REVIEW OF RECENT LITERATURE

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INTRODUCTION

WITH the increasing complexity of modern civilization the incidence of gastroduodenal ulceration appears to be on the increase.¹ Peptic ulcer² is most frequently a disease of the third and fourth decades of life but may occur in infants or even in the very old.^{3,4,5} Ivy (1946)⁶ stated that between 5 and 12 per cent of the population can be expected to be afflicted with this disease at some period during the life span. Whereas 100 years ago most of the ulcers seen in autopsy material were said to be gastric ulcers today the great majority of ulcers seen both by the clinician and at autopsy are on the duodenal side. Moreover, there appears to have been a change in sex ratio during the last century: benign ulcers are seen less and less frequently in women and are becoming much more common in men. This fact is of obvious economic importance because by incapacitating the breadwinner of the family, the disease can cause severe economic hardship for that particular group.

Allen and Welch (1942-1946)^{7,8} estimated that 15 to 20 per cent of the patients admitted to the Massachusetts General Hospital with a diagnosis of duodenal ulcer require surgical treatment sooner or later and the figures for other institutions are in relatively close agreement. There is a growing feeling expressed by numerous writers on the subject^{9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100} that gastric ulcer, diagnosed clinically if it does not heal promptly with medical therapy, becomes primarily a surgical problem because of the possibility of the presence of an unrecognized carcinoma. With these considerations in mind some idea of the frequency of operations for peptic ulcer is obtained and it becomes immediately obvious that it is extremely important for the gastric surgeon to determine what constitutes a satisfactory operative procedure for benign ulcer. The history of gastric surgery is traced by Finney¹ in 1929 and the profusion of literature on the subject since that time both show that the methods of choice are constantly changing.

The recent reintroduction and popularization by Dragstedt (1943 to 1945)^{122,123,124} Grimson (1947)¹⁹² Moore and associates (1947)^{26,27,28}

This paper represents a portion of a thesis presented to the Graduate Faculty of the University of Virginia in Candlish's fourth Degree of Master of Science.

The term "peptic ulcer" will be used throughout to denote gastric, duodenal and marginal ulcer. While this seems to presuppose a common etiology it should be borne in mind that they may be different diseases.

of vagus resection as a mode of surgical therapy for peptic ulcer has acted as a strong stimulus for the reevaluation of all previously used procedures for ulcer in numerous surgical centers

A further stimulus toward study of the entire subject has been the introduction, by Code, Varco, Wangensteen, and their associates (1940-1942),^{92 212 490 494} of an experimental method consisting of the daily injection of a histamine beeswax mineral oil mixture, by which gastric and duodenal ulcers can be produced almost at will in dogs and other experimental animals without the use of deforming surgical procedures which may cause grave changes in the physiology of the animal. This method has already proved useful not only in the further study of the etiology of peptic ulcer but in the evaluation of various surgical procedures used in the therapy of peptic ulcer. It is reasonable to assume that operations which will protect dogs against the histamine induced ulcer should prove efficacious and perhaps curative in dealing with peptic ulcer in man.

If the surgeon is not to become an artisan who operates at the behest of the internist it is essential that he understand (1) the physiology of the organs involved (2) what is known of the etiology and pathologic physiology of the disease he is attempting to treat, (3) what should constitute the most satisfactory procedure in the individual case under consideration (4) the physiologic and clinical results which such an operation can be expected to produce (5) the probable mortality rate of the operation chosen and (6) complications which may ensue and particularly methods by which those complications may be avoided. With regard to ulcer surgery, these considerations are detailed in a great mass of literature. I felt that it would be of some value to review enough of this literature so that a synopsis could be presented concerning (1) gastric physiology (2) theories of ulcer genesis (3) various operations for ulcer and (4) postoperative physiology. The emphasis will at all times be placed on gastric resection the operation which has so far withstood the test of time better than any other. Wangensteen who is unusually well informed on the subject

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his entire lifetime in the enviable  
with gastric physiology and peptic  
ure has been covered, and most of

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the important ideas dealing with the subject matter outlined here have been assimilated. In this process numerous contradictions become apparent both in the physiologic and in the surgical fields, which cause considerable difficulty in an evaluation of this literature. There are a number of reasons for this. A tremendous amount of work has been done on a variety of experimental animals all of which may not be similar physiologically to man and some of which (for example the rat) are certainly not similar to man with regard to gastric anatomy. Particularly in the study of gastric secretion such a wide variety of test meals have been used that the results of various workers are not comparable and the conclusions in many cases not valid. Many observations are uncontrolled and in some cases there is a possibility that the observations themselves may have been faulty. On the clinical side a few writers indicate

a lack of knowledge of the basic physiology involved others overeagerly draw conclusions from insufficient or statistically insignificant data. In some cases, the writings of clinical surgeons tend to be colored by their own pre-existing ideas or prejudices. Thus it should be borne in mind that the literary review to be presented should be accepted with certain reservations.

GASTRIC PHYSIOLOGY

Anatomy and Physiology

The stomach, for practical purposes may be divided into a (1) narrow cardiac zone just below the cardiac sphincter (2) a fundus which consists of the upper convex portion (3) a corpus which constitutes the great body of the organ and (4) a pyloric antrum which is that narrowed segment just proximal to the pyloric sphincter.

The stomach is a vascular organ and gets its blood supply from four large arteries (the left and right gastric on the lesser curvature and the left and right gastroepiploic on the greater curvature) all of which originate in the celiac axis. The anastomoses between the many branches of these vessels are numerous and Irvine and Bergh (1943)⁹ found that ligation of two or three of the large arteries supplying the stomach of the dog was possible without alteration in the gastroscopic appearance of the gastric mucosa. If all four arteries were ligated the dogs died of peritonitis resulting from necrosis of the stomach wall. These workers found that ligation of two or three of the large arteries produced no significant change in gastric secretion. On the other hand Leveen (1948)²⁹⁸ found that by ligation of the left and right gastroepiploic the vagi brevia and the right gastric artery in dogs, there was some degree of protection against histamine induced ulcer and he concluded that the energetic requirements for secretion were reduced by the decreased blood flow, thus diminishing the acid secreted. The figures given in his few studies of secretion before and after operation do not appear to be of sufficient significance to support this conclusion. In some dogs ulceration was produced in the stomach by excessive devascularization. Somervell (1945)⁴³⁹ has utilized a similar idea as a basis for the advocacy of a partial devascularization of the stomach as an operative procedure useful in the treatment of peptic ulcer. Reeves (1920)⁴⁴⁴ made an extensive study of sixty-two fresh human stomachs from autopsy material with examination of the blood supply of the stomach and duodenum by means of gelatin carmine injection through the celiac axis. He found that the lesser curvature of the stomach and the first inch of the duodenum were less vascular than other portions of these organs and that in these regions the anatomic arrangement of the smaller vessels is such that there is a predisposition to stasis and thrombosis.

The mucosa of the stomach is thrown up into deep folds and rugae except in the region of the lesser curvature and pyloric antrum and moves freely over the muscularis. Scott (1929)⁴⁴⁴ found that the measured surface area of the mucosa of the average adult stomach was 525 cm. In the lesser curvature region Aschoff (1924)⁴⁰ noted that there were four longitudinal folds, but that

there were no convolutions as in the rest of the stomach, and he called this the "Magenstrasse" or gastric pathway feeling that this was the normal course taken by a food bolus. Moreover the mucosa in the lesser curvature and antral region is much more adherent to the muscularis than elsewhere. Wangensteen (1947)⁵⁰⁹ felt that these anatomic facts are partially responsible for the occurrence of most benign gastric ulcers in these areas.

The stomach is supplied by parasympathetic nerves (the right and left vagus) and by sympathetic nerves of splanchnic origin. There are two intramural plexuses in the stomach. The myenteric (Auerbach's) plexus contains nerve cells in groups or ganglia connected by nerve bundles containing both intrinsic and extrinsic fibers. The submucous (Meissner's) plexus contains very few ganglion cells but its fibers communicate with those of the myenteric plexus. Some consideration as to the function of this nerve supply will be given in the discussion on gastric secretion and motility.

There are four types of secretory cells in the gastric mucosa, according to Hollander (1937).⁹ The mucous cells of the surface epithelium are thought to secrete a viscous mucus. The peptic cells (chief cells of the body of the gland (parietal, or adenomorphous cells) secrete proteolytic enzymes. The parietal cells (acid oxyntic adenomorphous cells or Belegzellen) secrete hydrochloric acid. The product of the chief cells of the neck of the gland (or mucoid cells) is unknown although Babkin (1944)⁹ felt that they probably secrete a viscous mucoid substance. There is some evidence that upon occasion certain of these cells may become transformed to other types of cell. Harvey (1906)²¹⁰ by histologic studies, noted that after gastroduodenostomy in dogs the body chief cells in the region of the anastomosis were transformed into mucous forming cells. One month after operation a reversal of this transformation occurred.

These various types of secretory cells are not uniformly distributed throughout the gastric mucosa. Harvey¹⁰ noted that there were no parietal cells in the pyloric antrum of the canine stomach. Miyagawa (1920)³⁸⁴ studied the exact distribution of the various types of cells in human stomachs. He noted that there were three types of gastric glands: (1) The cardiac glands, which secrete chiefly mucus and contain only a few parietal and peptic cells are limited to a narrow area immediately around the esophageal orifice. (2) The pyloric zone the area of which could be determined by describing an arc the center of which was at the pyloric end of the lesser curvature with the radius equal to 3/10 of the length of the lesser curvature contains glands which consist chiefly of mucus producing cells with only a few oxyntic cells. Miyagawa doubted if the latter secreted any acid. (3) The fundic glands contain all types of secretory cells. Berger (1934)⁵ made a thorough study of the exact distribution of parietal cells in the human stomach and found that there were practically none in the pyloric zone the greatest number in the major portion of the fundus while in the upper portion of the fundus and the cardia the number of parietal cells is considerably reduced (Fig 1). Aschoff (1924),⁹ like Berger and Miyagawa observed that the pyloric zone extends a considerable distance further on the lesser curvature side than it does on the greater curvature side and noted an

intermediate or transition area between the pyloric and fundic zones. This and other work has been summed up by Babkin (1944) ² in the schematic representation in Fig. 2. This histologic evidence has received abundant support in the experiments of Ivy (1919), ²²⁹ Ivy and Odam, (1921) ²³² and Lam and Dott (1923) ²⁰⁹ all of whom worked with isolated pyloric segments in dogs and found that the secretion of such a segment was thick, viscid and slightly alkaline (pH 7.0 to 7.5). Ivy and Odam noted no substance of digestive importance but Lam and Dott observed some evidence of proteolytic activity (pepsin) in the pyloric secretion. By utilizing innervated and denervated pyloric pouches, these workers were able to conclude that the pyloric secretion was mediated to some extent through the vagus nerve. McCrea and McSwiney (1926) ²⁴² also

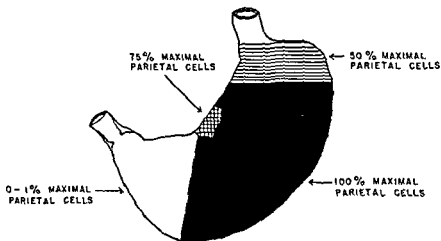


FIG. 1—Distribution of parietal cell in stomach (after Hergert)

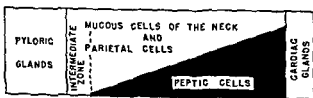


Fig. 2—Schematic drawing of distribution of different types of cells in the gastric mucosa (after Babkin)

studied the secretion of isolated pyloric segments in dogs after sectioning the vagus in the neck and determined by the use of variable stimuli to the distal cut ends of the vagi that depending on the strength of the stimuli secretory activity was increased or inhibited. Curiously despite this incontrovertible evidence an occasional article is encountered ^{2, 3} in which the claim is made that by doing a partial or subtotal gastrectomy all the acid secreting tissue is removed from the stomach.

Gastric Secretion

While the secretion of hydrochloric acid by the parietal cells has been studied in great detail the other components of the gastric juice have not been

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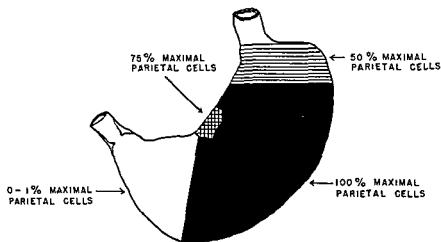


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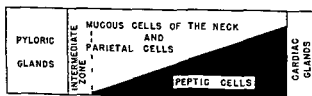


Fig 2—Schematic drawing of distribution of different types of cells in the gastric mucosa (after Lubkin)

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Gastric Secretion

While the secretion of hydrochloric acid by the parietal cells has been studied in great detail, the other components of the gastric juice have not been

studied so thoroughly. The alkali component consists chiefly of pepsin, mucous rennin, and lipase.³³⁴ For a comprehensive review of the subject, including details of physicochemical and histochemical studies the reader is referred to the excellent work of Babkin (1944).³³⁵ Schiffrin and Ivy (1942)⁴⁴¹ have reviewed the subject in a more concise manner. With regard to the existence of an interdigestive or continuous secretion, the opinion is not uniform. Concerning the digestive period of gastric secretion all authorities are in agreement that it may be divided into cephalic, gastric and intestinal phases.

Interdigestive or Continuous Secretion—Pavlov (1910)³³⁷ in his studies on dogs with gastric fistulas felt that there was no secretion of acid gastric juice except in response to psychic stimuli or food. He observed that great pains were necessary to avoid any psychic stimuli and thus achieve absolutely basal conditions. Carlson (1923)³³⁸ determined in a man with a gastric fistula that there was a continuous fasting secretion of 10 to 60 cc per hour; he felt that there was no true hypersecretion, but that apparent hypersecretion is due to pyloric dysfunction. Wolf and Wolff (1943)³³⁹ found that the fasting stomach of their fistulous subject secreted acid juice at a constant rate (10 to 15 cc per hour). Winkelstein (1935),³⁴⁰ studied the secretion of gastric juice at night in a large number of normal individuals and individuals with benign ulcer and found that the normal subjects secreted little or no hydrochloric acid during the night while those with ulcer secreted a large volume of highly acid juice. Dragstedt made similar observations^{118, 119, 123} and ascribed the beneficial effect of vagus resection to a diminution of this excessive interdigestive secretion. Thornton Storer and Dragstedt (1946)⁴⁴² have shown that it is tremendously reduced after vagus resection. Babkin (1944)³³⁵ noted an interdigestive acid secretion in normal individuals who were shielded from psychic stimuli of any sort. To some extent this idea is supported by Ivy (1941)³⁴³ and Schiffrin and Ivy (1942)⁴⁴⁰ who noted that the interdigestive secretion is abolished in normal individuals by the use of atropine. It is interesting that the 'hypernormal' secretion of ulcer patients is not abolished by the use of this drug which makes Ivy feel that possibly this immoderate secretion is due to the excessive production of histamine by irritated gastric mucosa. Bloomfield (1940)³⁴⁴ has observed that patients with duodenal ulcer secrete under basal conditions a larger volume of highly acid gastric juice than is ever obtained by normal individuals. Recently Sindewicz, Suzerman and Podolsky (1946)⁴⁴³ have made similar observations but conclude that this is due to delayed emptying of the stomach.

The Psychic (Cephalic) Phase of Gastric Secretion—The classic experiments of Pavlov (1910)³³⁷ and his group on dogs with esophagotomies and gastric fistulas showed quite conclusively that acid gastric secretion occurs in approximately five minutes in response to the sight, smell or taste of food and even to such conditioned stimuli as the appearance of the attendant who customarily fed the animals. It really that by section of the vagus nerve, showing that it is mediated through the vagus. This phenomenon was noted by Beu-

mont and studied in detail by Wolf and Wolff (1943)⁴¹ who found that this psychic secretion was profoundly influenced by the emotional state of the fistulous subject studied. Thus fear caused a hypoxemia of the gastric mucosa and hyposecretion while resentment or embarrassment caused a hyperemia of the gastric mucosa and hypersecretion. This psychic phase of secretion is extremely variable depending on the individual and the type of stimulus,⁴² but Ivy (1941)⁴³ believed that an average volume of this secretion is 50 to 150 cc during a period of twenty minutes. Vineberg (1931)⁴² felt that the various secretory cells were supplied by different fibers of the vagus nerve, since he found that the secretion of various elements was activated at different thresholds of electrical stimulation of the vagi in dogs. Vineberg and Babkin (1931)⁴² found that pilocarpine (a parasympathetic stimulator) activated chiefly the production of the inorganic substances and enzymes of the gastric juice while administration of histamine in conjunction with pilocarpine was necessary to produce a relatively normal secretion. Baxter (1932-1934)⁴²⁻⁴³ studied the role of the sympathetic nervous system in gastric secretion in dogs and cats and concluded that the splanchnics have a very definite relationship to the mucoid elements of the gastric mucosa but play no essential part in the cephalic phase of secretion.

Hartzell (1929)⁴⁴ sectioned the vagi of dogs in the thorax and found that there was a marked reduction in the free and total acidity of the gastric secretion after this procedure. In view of the present popularity of vagus resection, Van Zant's work (1931)⁴⁵ is worthy of note. Using some of the same dogs that Hartzell had vagotomized two and one half years previously she found that the secretion in all four of the dogs studied had returned to approximately normal levels. She postulated that the stomach developed a degree of autonomous control the mechanism of which was unknown. Likewise Shipiro and Berg (1934)⁴⁶ after making Pavlov (innervated) pouches in dogs for use in the analysis of the gastric secretion did subtotal gastrectomy with complete division of the vagi below the diaphragm. They found a temporary diminution in the acid secretion of the pouches which lasted twelve to thirty three days but subsequently this secretion returned to normal levels. This was thought due to an autonomous gastric compensatory mechanism the seat of which was in the plexuses of Meissner and Auerbach.

The possible influence of the parasympathetic nervous system on ulcer development and its direct clinical application will be discussed in more detail later.

The Gastric Phase of Secretion—With the actual arrival of food in the stomach the second or gastric phase of secretion is initiated. In normal man Ivy (1941)⁴³ stated that this averages 225 to 300 cc for a period of approximately five hours but it may vary considerably in different individuals⁴⁴ with regard to acidity and volume. There is practically no absorption of foodstuffs in the stomach and the quality of gastric juice varies considerably with the type of food. Thus as Pavlov³⁹ showed years ago a protein meal will call forth a higher volume and acidity than a meal composed chiefly of carbohydrates.

Pavlov found that secretion of gastric juice was not stimulated by mechanical irritation of the mucosa or distention of the stomach wall, and similar observations have been made by Wolf and Wolff (1943)³²⁴ on their subject with a gastric fistula. Other authorities, such as Schiffrin and Ivy (1942),⁴⁴⁰ quoted work in which gastric secretion was provoked by mechanical distention of the stomach with balloons. The secretagogue effect of food may be the result of substances present in the food (especially in lean meat liver etc.) or those arising as products of digestion, such as peptones and fatty acids. Babkin (1938)² felt that gastric secretion is in part due to the vagal impulses as a result of cerebral stimulation due to the hypoglycemic state of a hungry individual, but this phenomenon should better be considered as a part of the psychic phase of secretion. As the stomach empties the gastric and intestinal phases of secretion overlap to some extent. The possibility of the existence of a hormonal mechanism in the gastric phase of secretion is of such clinical and surgical importance that this will be considered in greater detail.

The gastrin theory. In 1906, Edkins¹²¹ found that extracts of the pyloric mucous membrane of cats and pigs made by boiling with dilute hydrochloric acid, when injected intravenously into an animal, led to secretion of acid gastric juice. Extracts of the fundic mucosa however made did not have this property. Moreover, the secretion produced by these extracts could not be diminished by the administration of atropine. He postulated that the pyloric mucosa contained a substance, which he called gastrin which was liberated into the blood stream as a result of the action of foodstuffs and thus produced acid gastric secretion. The experiments of Edkins touched off a physiologic controversy which is as yet far from settled.

[Edkins and Tweedy (1908)¹²² inverted pulley shaped balloons into the stomachs of cats. By tying a ligature around the stomach over the groove of the pulley, they separated the pyloric region of the stomach from the fundus. In acute experiments using cannulas they were able to demonstrate that meat extracts and other substances when introduced into the duodenum or pyloric portion of the stomach caused a marked secretion of acid juice from the fundus but when similar substances were introduced into the fundus there was no evidence of secretion. Gross (1906)¹²³ working in Pavlov's laboratory came to similar conclusions.]

Popielski⁴⁰² called attention to the general distribution in numerous tissues such as brain gastric and intestinal mucosa and pancreas and the presence in Witte's peptone of substances which cause vasodilatation when injected intravenously, and which also cause a more active secretion of all the digestive glands in general. He called such a substance *vasodilatin* and thought that the secretagogue effect was due to vasodilatation and not to a specific effect on the secretory cells. Popielski explained Edkins' negative findings with extracts of fundic mucosa as being the result of an overdose of vasodilatin. Keeton and Koehl (1915)²⁴⁴ found a similar substance in the brain throughout the gastric mucosa and in smaller concentrations in the duodenum. Injection of this substance would produce a fall in blood pressure. This substance was assayed

using animals with Pavlov gastric pouches and they concluded that it caused true gastric secretion rather than a secretion resulting merely from vasodilatation.

Pavlov (1910)²⁹ accepted Edkins' theory, and his work was further substantiated by the work of Lim (1922)^{30a}. It was shown by Lim and Ammon (1922)³⁰ that if pyloric extracts were injected into the portal vein the secretory effectiveness was less marked, apparently due to a removal by the liver of a portion of the gastrin. Ivy and Whitlow (1922)²⁴ felt that the experiments of Edkins and Tweedy were uncontrolled and on repeating them with modifications they obtained negative results. Using animals provided with a Pavlov pouch and a small pyloric pouch both of these being separated from the main stomach these authors were unable to obtain any increased secretion from the Pavlov pouch when test meals were inserted in the pyloric pouch.

✧ However at a later date, Ivy and his co-workers (1925)⁹ felt that they had demonstrated by means of cross-circulation experiments between starved dogs and recently fed dogs both with and without the injection of gastrin that a humoral mechanism was probably concerned in the genesis of gastric secretion. This humoral mechanism was demonstrated more conclusively²⁴ by means of the transplantation of a fundic pouch to the subcutaneous tissue with severance of the normal blood supply after blood supply had developed from surrounding tissues. When such a dog was fed there was an increase in the volume and acidity of the pouch secretion. However it was noted that the stimuli had to be more intense to evoke secretion than those necessary with a Pavlov (inner vated) or Heidenham (denervated) pouch.

✧ Some doubt was cast on Edkins' hypothesis by Portis and Portis (1926),^{40a} who did subtotal gastrectomies on dogs previously provided with Pavlov pouches and found that the pouches continued to secrete a considerable amount of acid juice. Wilhelmj O'Brien and Hull (1936)^{32a} compared the acid secretion of two dogs before and after partial gastrectomy with that in two dogs before and after gastroduodenostomy. Their experiments as well as those of McCarthy^{34a} indicated that removal of the pylorus lowered the acid secretion more than could be accounted for by the diluting and neutralizing effect of the duodenal secretions. Moreover a comparison of the gastric secretion from four animals with whole stomach pouches including the pylorus with that from five animals in which the pyloric antrum had been removed from the pouch showed that the acid secretion was markedly lowered by removal of the antrum. Enderlen and Zuckerswerdt (1931)³² noted that one year after resection of the antrum in dogs the second phase of gastric secretion had returned to normal levels. They thought that a readjustment occurred whereby the small intestine took over the function of the pylorus.

✧ Priestley and Mann (1932)⁴² working with dogs did a transection of the stomach thus excluding the antrum accompanied by a gastrojejunostomy. At a later operation the antrum was resected. Observations were made on gastric acidity before and after each procedure. While the first procedure lowered acidity somewhat, the second procedure had no effect on acidity, and they there

fore concluded that in dogs the pyloric mucosa was not an important factor in gastric acidity. These same workers prepared one series of dogs by isolating pyloric pouches, making gastrojejunostomies and establishing fistulas to both the fundus and pyloric pouch, by using intraperitoneal segments of ileum. Another series of animals was prepared in the same way except that a fundic pouch was also created and transplanted to the exterior. In the first series of animals, beef extract placed in the pyloric pouch caused secretion in the fundus (although they attributed this to the psychic influence of smelling the extract). In the second series this did not occur. In both series of animals hydrochloric acid or gastric juice placed in the pyloric pouch failed to evoke any secretion from the fundus. It is unfortunate that they chose these substances as test meals since, as will be developed in this paper, acid exerts a very definite inhibitory effect on gastric secretion.

Klein (1932)² prepared a gastric pouch from the mucous membrane and submucosa of the stomach and transplanted it into the subcutaneous tissue where it developed a new blood supply. Such a pouch although devoid of vagus or sympathetic innervation without its normal blood supply and denuded of Auerbach's plexus responded to the presence of food in the main stomach by the secretion of gastric juice containing pepsin and hydrochloric acid thus indicating a hormonal influence. Lewis (1933)²⁹ excised the antral mucosa in dogs making an anastomosis between the mucosa of the corpus and that of the duodenum without removing any of the muscular or serous layers. He found that after such a procedure there was a marked diminution in acid response to a test meal, although the emptying times remained the same. Edkins' hypothesis was further supported by the work of Bihkin (1934)²³ who in experiments with pyloric pouches obtained results diametrically opposed to those of Priestley and Mann. Also in dogs equipped with Pavlov pouches, gastric fistulas and duodenal fistulas with separation of the antrum from the remainder of the stomach, introduction of meat extracts into the fundus failed to produce secretion from the pouch or fundus but if similar dogs were prepared with the whole stomach separated from the duodenum (that is without separation of the antrum), the secretory response of both Pavlov pouch and main stomach was strong in response to the ingestion of the same materials. Morrison (1938)³⁰ using neutral red as a specific test of oxyntic cell activity concluded that this activity is regulated by a pyloroduodenal hormone.

Sacks and others (1932)³¹ have shown that the gastric secretory effectiveness of acid extracts of the pyloric mucosa of dogs is inactivated by histaminase and they concluded that histamine is the sole secretory excitant in so-called "gastrin" preparations. However they emphasized that they had not proved that histamine was the gastric hormone nor was it proved beyond doubt that there was a gastric hormone. Histamine has been isolated from the stomachs and intestines of several animals⁶¹ and from the gastric mucosa (both fundic and antral) in men.⁶² Bihkin (1934)²³ has shown that secretin and histamine are not identical but gastrin and histamine have not been separately identified chemically.

✱ The experiments of GILSON and ILL (1941)²¹⁸ with dogs with two and three pyloric pouches demonstrate conclusively that a hormonal or humoral factor is concerned but they found that the pyloric mucosa was not the sole site of the hormone since the presence of secretagogues in the fundic pouch caused acid secretion in the pouch transplanted to the subcutaneous tissue. The possibility must not be overlooked in these and many similar experiments that the fundic pouches may have contained small areas of antral mucosa. Recently KOMAROV (1942)²¹⁹ has repeated Edkins' first experiments with almost identical results.

✓ From this mass of experimental evidence it seems valid to conclude only that there is a humoral mechanism concerned in gastric secretion. Whether the hormone is identical with histamine and whether the hormone is localized chiefly to the pyloric mucosa remains to be determined. There certainly is considerable clinical evidence supporting Edkins' thesis. At least we know that patients with a Finsterer exclusion resection without removal of the antral mucosa tend to develop jejunal ulcer² or the antral syndrome.³⁶ WANGENSTEEN^{200, 212} after a study of the experimental and clinical evidence accepted the gastrin hypothesis chiefly as an augmenting factor in gastric secretion but not as an initiating factor and noted²⁰⁶ that some doubt is cast on such a theory by the development of jejunal ulcers after pylorectomies.

✓ *The Intestinal Phase of Secretion*—ILL and McILVAIN (1923)²²¹ prepared Pavlov pouches in dogs and at a later date made fistulas by transecting the duodenum distal to the pancreas and transecting the jejunum distal to the ligament of Treitz. One end of this segment of bowel was brought out through a stab wound to the body surface and the other end closed. Continuity of the gastrointestinal tract was re-established by a duodenojejunosomy. They studied the secretion of the Pavlov pouches obtained in response to substances introduced into this intestinal fistula and found that acid secretion was evoked by a considerable variety of substances thus proving the existence of an intestinal phase of secretion. This phase has been studied in a slightly different manner by ILLUM and MCCARTHY (1925)²²⁰. They found in a dog in which the entire stomach was formed into a pouch and continuity re-established by an esophagoduodenostomy that the feeding of secretagogues by mouth resulted in acid secretion from the total gastric pouch after a latent period of 1 to 3 hours. On the other hand undigested food would not stimulate such a secretion and it is generally agreed that gastric secretion in the intestinal phase is due to the secretagogue action of the products of digestion (such as peptones and amino acids). As previously stated the intestinal phase overlaps the gastric phase to some extent and the intestinal phase may last a considerable period of time depending on the type of food. With a high protein diet the intestinal phase of secretion may amount to 2 to 3 liters per day.²²⁰ There is some evidence that the intestinal phase is mediated through the vagi since it is inhibited by the administration of atropine.²²

✓ *The Control of Gastric Acidity*—There are a number of quite different theories of the mechanism by which hydrochloric acid is secreted in the stomach.

most of which are mentioned by Babkin (1944)¹⁰ along with the physicochemical evidence involved. Perhaps the two most important are those of Rosemann (1907)¹¹ and Pavlov (1910)¹². Rosemann thought that the total chloride of the gastric juice was constant but that the acidity was variable in the juice as secreted. This variability in acidity was thought due to (1) an accumulation of neutral chloride in the gastric mucosa and (2) a formation of hydrochloric acid from the neutral chloride. The oxyntic cells were assigned (by Rosemann) the capacity of concentrating chloride to a higher level than that in the blood or lymph and then combining it with H^+ ion. In true anaecidity, he thought the total chlorides were secreted in the form of neutral chloride.

✓ The theory more generally accepted by physiologists today is that of Pavlov who held that the gastric juice as secreted always possessed the same degree of acidity 0.5 per cent or 16 N HCl which is isotonic with the blood. Babkin¹³, Dragstedt¹⁴, Hollander,¹⁵ Wilhelmj¹⁶, Wolf and Wolff¹⁷ and other eminent physiologists are in essential agreement with this theory. The details of how this idea was arrived at need not concern us here.

✓ If it is true that the hydrochloric acid in dog and man occurs at a concentration of 0.5 per cent how can it be explained that the average acidity of gastric contents is found¹⁸ to be in the neighborhood of 0.2 per cent HCl? Moreover it is known¹⁹ that after the initial secretory period there is a rapid fall in acidity and this merits some explanation. Pavlov¹⁹⁷ observed that 'the first duty of intestinal digestion is to convert the acid medium of the stomach into an alkaline or neutral one in the bowel'. Boldyreff (1914)²¹ went further than this and elaborated a theory as to the self regulation of gastric acidity. As a result of experiments on dogs in which 0.5 per cent HCl was introduced

HCl this partial neutralization being due chiefly to a reflux into the stomach of alkaline juices from the duodenum. The pancreatic juice was thought to be most important as a neutralizing agent since the prevention of the entrance of bile (by cholecystoenterostomy and ligation of the common duct) or of saliva (by means of an esophageal fistula) into the stomach resulted in very little change in neutralization of the acid test meal. When the pancreatic ducts were ligated the body responded with an excessive flow of bile and succus entericus to aid in neutralization. Boldyreff also found that when neutral or alkaline fluids were introduced into the stomach the organ responded by an excessive secretion of acid to bring the acidity up to normal levels.

✓ This theory has received considerable opposition in certain quarters. MacLean and Griffiths (1928)²² concluded as a result of acid test meals and fractional analyses in human subjects that the gastric glands secrete at all times a juice of constant chloride concentration in which the relative amount of basic (Na^+) and acid (H^+) ions in combination with the chloride ion were varied according to the requirements of the stomach. This differed but little

from the theory of Rosemann. They discounted the possibility of regurgitation of duodenal contents as an important factor in neutralization because of the absence of trypsin in most specimens of gastric juice. To quote their work:

The presence of a certain concentration of acid in the stomach inhibits secretion of acid with the result that a neutral fluid containing chloride is secreted, which by dilution, reduces the acidity of the gastric contents." The studies of Griffiths (1936)³² with tubes in both stomach and duodenum showed that the secretion of acid by the stomach was inhibited by the introduction of weak hydrochloric acid into the duodenum. It was suggested that the acidity of the gastric contents entering the duodenum may be the important factor in the control of gastric acidity during the normal digestion. Shay and others (1942)⁴³ came to similar conclusions. McCann (1929)³³ in his studies on emptying time, felt that he had disproved Boldyreff's theory of alkaline regurgitation. He thought two factors were responsible for neutralization: (1) a gradual reduction of the established high rate of secretion of acid to a low one, and (2) the capacity of the constant basal secretion of mucus to combine with a constant fraction of the changing volume of acid secreted.

Shay and his co-workers (1932)⁴⁴ studied human subjects by administering bromsulfalein intravenously followed by an acid test meal and fractional analysis. They found that while duodenal regurgitation does take place there was no correlation between the concentration of dye in the stomach and the reduction in acidity and the conclusion was therefore reached that Boldyreff's theory lacked validity. This theory was further questioned by Kessler and Mann (1943)²⁰ who isolated the duodenum in dogs and closing one end drained the other end by anastomosis to the fundus re-establishing continuity by a gastroyejunostomy. On comparing acid values of fundic pouches or of the stomach (by means of antiperistaltic fistulas made from loops of ileum) before and after such a procedure they found that the acidity of the fasting stomach was not reduced by this procedure although bile was always found in the stomach, and in many cases the volume and acidity of gastric secretion was higher than it was before. Since the entire duodenal contents could not cause effective neutralization and buffering of the gastric secretion they doubted that regurgitation of duodenal contents was an important mechanism in neutralization of gastric acidity.

However the evidence in favor of this mechanism is considerable. A study was made of the trypsin in the fasting gastric contents of thirty-four human subjects by Spencer, Meyer, Relifson, and Hawk (1915)⁴⁵ who found trypsin absent in only two of the thirty-four individuals. Moreover with the introduction of acid into the stomach of these patients the trypsin values immediately rose but when water or alkaline solutions were introduced the tryptic values remained low. The tryptic enzyme was thought to be regurgitated from the duodenum. The importance of pyloric relaxation in this regurgitative phenomenon was emphasized by Polton and Goodhart (1922)³ who noted that in ulcer patients with pylorospasm or with pyloric stenosis such regurgitation failed to occur resulting in hyperacidity. In normal individuals as the curve

for hydrochloric acid concentration went down the curve for inorganic chlorides went up, presumably due to regurgitation and neutralization by duodenal juices but this was not so apparent in ulcer patients. Antiperistaltic movements of the duodenum promoting regurgitation of duodenal contents has actually been demonstrated^{14, 17} by roentgenologic means.

Burget and Steinberg (1922),²¹ working with dogs, found that regurgitation of duodenal contents into the stomach occurred regularly within thirty to forty five minutes after introduction of 100 to 150 c.c. of 0.5 per cent HCl, and the acidity of the stomach contents was reduced to 0.1 to 0.15 per cent HCl in seventy five to ninety minutes. Apperly (1926)¹⁷ studying the control of the pylorus thought that any chyme propelled into the duodenum which was not of a certain acid and salt value was promptly re-regurgitated back into the stomach until that value was reached. Rehfuess and Ladd (1929),⁴¹² employing balloons in both the stomach and duodenum of medical students observed that in fasting stomachs there were periods during which increased duodenal tonus and increased motor activity in the duodenum were conducive to regurgitation. This activity did not correspond to that of the antrum. Evidence of early duodenal regurgitation was found in seventy two per cent of forty six subjects on whom fractional analyses after acid test meals were performed by Apperly and Norris (1930).¹⁸ These authors attributed more importance to the factor of dilution than to the factor of neutralization in the lowering of gastric acidity.

It is known that deviation of the duodenal contents to the lower gastrointestinal tract by preventing such a regurgitative phenomenon results in an elevated gastric acidity³² in dogs. The role of the pylorus in this process of regurgitation was dramatically demonstrated by the experimental work of Elman and his group (1931-1933).^{130, 141} If pyloric insufficiency was produced by cutting the sphincter a persistent lowering of gastric acidity followed, and there was augmented neutralization of acid test meals administered to the dogs. On the other hand when partial stenosis of the pylorus was artificially produced the acid test meals administered to these dogs were incompletely neutralized. Isj, Droegmueller and Meyer (1927)² obtained essentially similar results with artificial pyloric stenosis in dogs. Medoff and his colleagues (1941)³⁴⁹ were unable to demonstrate consistently any change in acid values after production of partial pyloric obstruction but their work was seemingly invalidated by their own observation that the emptying time of these supposedly obstructed stomachs was not materially affected.

While theorizing as to the important mechanism in the control of gastric acidity whether it be a result of the regurgitation of duodenal contents or an expression of a variability in the acid concentration of the gastric juice as secreted it is well to remember that there are other less important mechanisms concerned in the dilution neutralization and buffering of gastric acidity. The volume output and rate of gastric emptying are obviously important.⁴⁴³ Hollander (1937-1939)^{20, 21} believed that a 'dilution secretion' of nonacid fluid with a composition similar to blood plasma occurs from the neck chief cells. This theory is not widely accepted however. Saliva and certain foodstuffs have

a moderate neutralizing power and protein foods may bind up hydrochloric acid as combined acid.²¹ The importance of mucous secretion as a neutralizing agent has received some prominence.²²⁻²⁶ MacLagan (1934)²¹ in a statistical analysis of 389 fractional test meals, concluded that reduction in gastric acidity was due chiefly to the neutralization and dilution produced by the alkaline mucous secretion of the pyloric segment. Helmer (1934)²¹ thought mucus to be present in sufficient quantities in the gastric contents to account for the main variations in gastric acidity. This evidence has been utilized by Foulson (1931)²² as a rationale for his advocacy of the treatment of peptic ulcer by the administration of mucus. Kim and Ivy (1931)²³ have prevented the development of duodenal ulcers in dogs with biliary fistulas by the administration of mucus.

Inhibition of Gastric Secretion—Inhibition of gastric secretion may occur as a result of nervous, humoral or chemical stimuli or as a result of certain abnormal factors. Wolf and Wolff (1943)^{23a} have shown quite well in their fistulous subject that certain emotional states such as fear inhibit gastric secretion. Both the vagi and splanchnics contain inhibitory fibers through which such impulses are mediated. It has also been shown that excessive mechanical distention of the intestine will inhibit secretion from the stomach. Atropine has been found to decrease the volume of secretion resulting from histamine stimulation in man but does not affect the free acid concentration to any great degree.²⁴ Roberts (1925)^{24a} thought that part of this effect was due to parasympathetic inhibition. He found the free acid concentration reduced after atropine and this was thought due to relaxation of the pylorus and thus increased regurgitation of duodenal contents.

Pavlov (1910)²⁵ recognized that a fatty meal inhibited gastric secretion and prolonged the emptying time. Kosaki and Lim (1930)^{25a} demonstrated that the probable mechanism of this inhibition was the formation in the mucosa of the small and large intestine following contact with fat of an inhibitory substance which they called enterogastrone. Potent extracts of the *duodenal mucosa* have been prepared^{25b} which will inhibit gastric secretion in dogs and hope has been expressed that such substances will prove valuable in the medical treatment of peptic ulcer in man.^{25c} A similar substance called urogastrone, which has been prepared by Ivy's group (1940)^{25d} is found to reduce the human gastric secretory response to histamine with regard to volume, acidity and free acid.

It has been demonstrated by McLean and Griffiths (1928, 1936)^{26, 26a} that introduction of acid into the stomach inhibits the secretion of gastric juice.

Acid was an important mechanism in the regulation of gastric secretion. The latter group of authors found that the intestinal phase of secretion was not inhibited by $N/10$ HCl in the stomach but inhibition resulted when the acid entered the duodenum. Stevens, Segal and Scott (1940)^{26a} found that there was no effect upon gastric secretion when dilute

hydrochloric acid was introduced directly into the duodenum but the mechanism has been generally accepted by most authorities. This acid inhibition is known to fail⁴⁴ in the presence of excessively strong secretory stimuli, and particularly in the presence of the cephalic phase of secretion, and it is therefore thought that a nervous rather than a humoral mechanism is concerned.

Andrus, Loid and Stufko (1942-1944)^{13, 14, 31, 313, 453} found that in dogs perfusion of the stomach with washings from an isolated jejunal loop caused a profound depression in the volume and acidity of gastric secretion. Moreover they found that when a segment of jejunum was implanted into the wall of the stomach keeping its blood supply intact, the pH of the gastric mucosa rose, and the secretory response to histamine was reversed (that is the volume and acidity of the secretion diminished instead of increasing). The effect was greater than could be accounted for by neutralization of acid with the alkaline jejunal secretion and it was thought to represent some type of inhibition of some phase of gastric secretion in which histamine played an important role. The exact mechanism concerned was not determined although Andrus felt it was not entero-gastrone. This procedure was found to protect against histamine induced ulcer in dogs although the series of dogs so tested was quite small. The experimental results were so promising that the pedicled jejunal graft was used as a mode of surgical therapy in a small number of ulcer patients, and the immediate results were gratifying with reduction in acidity in three of four cases. However, in the preliminary reports, none of these cases were followed more than nine weeks. The hope aroused by this work that such an operative method could be used as a means of producing inhibition of gastric secretion was promptly abated by the work of Grossman, Dutton and Ij (1945)¹⁰⁷ who found that neither perfusion of a gastric pouch with jejunal washings nor implantation of the pedicled jejunal patch into the gastric wall resulted in any significant change in the acid secretory response to histamine. Anderson, Slutsky, and Moertz (1945)¹¹ obtained similar results in their dogs. The results of Andrus and his group were also negated by Kolouch, Dubus and Wingensteen (1945)⁸² who found that such a procedure did not prevent the histamine induced ulcer in dogs nor did it reduce the secretory response to histamine. Saltzstein and Kurtz (1946)⁴³² have shown that this procedure fails to prevent the development of ulcer in Minn-Williamson dogs.

In addition to the factors resulting in inhibition of gastric secretion which have already been discussed there are certain abnormal conditions which depress gastric secretion. The acidity is decreased 85 per cent in pregnancy⁴⁴³ and it is interesting to note that peptic ulcer rarely occurs in pregnant women and if an ulcer is known to be present at the time of conception the clinical improvement during pregnancy is marked. Hyperglycemia and hypocalcemia apparently inhibit acid secretion as does deficiency in certain vitamins particularly thiamine and vitamin C⁴⁴⁰. Radiation of the stomach depresses gastric acid secretion to the point of achlorhydria after histamine³⁰³ and Palmer (1947)³⁶ has utilized this as the basis for treating peptic ulcer with x-ray.

✓ *The Composition of Gastric Juice*—In addition to hydrochloric acid, which has been quite well studied the gastric juice in man contains pepsin mucin, inorganic salts histamine rennin traces of lipase, and the so called intrinsic factor in the prevention of pernicious anemia⁴⁴⁰ Pollard and Bloomfield⁴⁴⁰ found that there was no correlation between pepsin output and acidity and thought their secretory mechanisms independent Vanzant and her co-workers (1932)⁴⁴³ studied the gastric acidity from 3746 cases and found that there was a tremendous variation in the normal acidity although it tends to decrease with age Because of this and other work Alvarez (1943)⁹ recently concluded that gastric analysis has little value as a diagnostic procedure except in connection with the anemias Similar observations were made previously by Bloomfield and Keifer (1926)⁴⁴ The analysis of gastric contents with the use of various test meals (Friedl alcohol etc) is somewhat colored by the dilution buffering and combining power of the test meal substance Such an objection is not valid with regard to histamine as a stimulus and so it may be considered the most reliable indicator of gastric secretion Alcohol is thought to stimulate chiefly the secretion of hydrochloric acid²² while pilocarpine and other cholinergic drugs activate the production of gastric mucus and enzymes Babkin (1938)²⁴ believed that stimulation of the vagi results in a liberation of histamine in the gastric mucosa and the histamine reactivates the parietal cells A hypoglycemic state results in the secretion of a juice of high acidity and peptic content and Babkin felt that the routine use of the insulin hypoglycemic test as outlined by Hollander (1946)²²⁸ for use in testing the completeness of a vagus resection would be a more accurate measurement of the gastric secretory capacity

Pepsin is reactivated by hydrochloric acid and is inhibited by products of its own digestion⁴⁴⁰ However, mucus inhibits peptic digestion possibly due to the adsorption of pepsin From the standpoint of this work the minimal digestive activities of rennin and lipase are unimportant

In summation to quote Babkin the secretory work of the gastric glands therefore is not regulated as a whole but the final product of this activity namely the gastric secretion is dependent especially as regards its composition, on the participation of various mechanisms nervous or humoral that stimulate (or inhibit) different parts of each gland

Histamine and Gastric Secretion—At this point since the use of histamine in testing gastric secretory function is so widespread and since it is used experimentally in the production of peptic ulcer it may be well to discuss briefly the relationship of histamine to gastric secretion A thorough review of the physiologic effects of histamine was contributed by Best and McHenry⁴⁰ in 1931 Histamine in considerable quantities has been obtained from canine gastric mucosa²² and from human gastric mucosa⁴⁴¹ In both species a secretagogue was found not only in the pyloric region but in the fundic mucosa which was inactivated by histaminase The possibility that histamine may be identical with gastrin has been suggested by Sacks and his co-workers (1932)⁴²⁹ but has not been proved

Parenteral administration of histamine results in a highly acid gastric secretion Lim and his co-workers (1923)⁴⁰⁹ and Pollard (1932)²⁹ found that

in human subjects histamine increased the rate of secretion and the amount of both acid and pepsin in the gastric juice. However Gilman and Cowgill (1930),¹⁷⁵ studying the secretion from Pavlov and Heidenhain pouches in dogs after the administration of histamine called attention to the fact that there was a progressive decrease in the pepsin concentration in the pouch juice from the level obtained shortly after the administration of histamine. This was thought due to a "washing out" of the glands by the newly secreted acid the original high level of pepsin being a reflection of the state of secretory activity of the chief cells before the histamine was administered. This work has been confirmed in dogs by Vineberg and Bablin (1931),⁴² and in man by Toby (1937).⁴¹⁹ Histamine is thought to act directly on the parietal cells, having a selective affinity for these cells the secretory response to histamine is not affected by vagotomy or atropine.⁶⁰ Some evidence has been presented by Alley (1935)¹ that histamine actually inhibits the action of the vagi on the peptic cells thus diminishing the secretion of pepsin. Histamine when prepared in a beeswax mineral oil mixture as done by Code and Varco (1940)⁴¹ and administered to experimental animals in doses varying from 15 to 60 mg daily will cause a marked increase in the volume and acid of gastric secretion within fifteen minutes after administration. This increased secretion was found by Code and Varco to persist for twenty four to forty hours although the maximum level was reached four hours after administration following which there was a considerable decline.

Motor Physiology of the Stomach

The motor physiology of the stomach is of course inextricably bound up with the mechanism of gastric secretion (but for the sake of clarity will be discussed separately). Quigley (1942)⁴¹⁸ has reviewed the subject rather thoroughly. The motor functions of the stomach in relation to food are (1) to store food (2) to break up the food mechanically (3) to mix it with gastric juice and (4) to move it forward. It has already been shown that appetite is a cerebral phenomenon. Appetite is associated not only with the cephalic phase of gastric secretion but with hunger contractions mediated through the vagi which occur as waves of peristalsis lasting about thirty minutes passing slowly from cardia to duodenum and followed by a relaxation period lasting about thirty minutes. These contractions are inhibited by the ingestion of food or by vagotomy but are augmented by splinchnicotomy.

When food enters the stomach the intragastric pressure falls with relaxation. The food is held chiefly in the fundus where it undergoes little mixing but is gradually reduced to a semiliquid state. Fats are melted proteins are attacked by pepsin and hydrochloric acid and starches partially digested by ptyalin. Periodically portions are broken off and pass to the pyloric antrum where they are broken up by powerful peristaltic waves which require thirty seconds to reach the pylorus from the incisura. Fluids usually leave the stomach one to four minutes after ingestion. With other foods the rate of emptying depends on the character and amount of the food the activity of the pyloric sphincter antral tonus etc. Fatty meals (through the medium of entero-as-

trone) inhibit motility as well as secretion and require a much longer time (six to seven hours) for emptying than meals poor in fat which require four to five hours.²² Other substances, such as excessive amounts of sugar, hydrochloric acid and peptones may also cause inhibition of gastric peristalsis. Certain emotional states such as worry may also inhibit gastric activity.

Pyloric achylasia resulting in interference with emptying of the stomach and regurgitation of duodenal contents is thought to produce stagnation and hyperacidity⁴¹² and is of considerable importance in the pathogenesis and pathologic physiology of peptic ulcer. Interest therefore has been centered on the mechanisms by which the pyloric sphincter is controlled. Forty years ago Cannon (1907)⁴¹³ elaborated the theory that the pylorus was controlled by acid concentration—that is that a high acid concentration in the pyloric antrum would cause opening of the sphincter and a high acid concentration in the duodenum would cause the sphincter to close. This theory which was further developed by the work of Apperly (1926)⁴¹⁴ and Shay and Cershon Cohen (1934)⁴¹⁵ was an attractive one to explain the gradual emptying of the stomach in a normal individual but as Hurst (1925)²³ pointed out did not explain why the pylorus is able to function in patients with achylia gastrica or why pyloro spasm occurs in association with gastric hyperacidity. Hurst felt that the hyperacidity was the result of the failure of the pylorus to open rather than the cause.

* [This subject will be developed more fully in the discussion of the relationship of acid peptic digestion to ulcer formation.]

It is known²⁴ that vagal stimulation causes contraction of the pylorus while sympathetic stimulation causes relaxation. Thomas and others (1934-1935)^{416, 417} found that acid in the region of the pylorus had little effect on the state of the sphincter and that the contraction of the sphincter was really a termination of antral peristaltic waves. Thomas thought that gastric emptying was regulated in part by a reflex inhibition of antral peristalsis due to duodenal stimulation. McCann (1929)²³⁸ felt that the products of protein digestion caused inhibition of the sphincter while undigested protein stimulated contraction. Werle and others (1941)⁴¹⁸ studied pressure gradients between the antrum and duodenum during digestion by means of intraluminal balloons and concluded like Thomas that contraction of the pyloric sphincter represented the termination of an antral peristaltic wave.

THE ETIOLOGY OF PEPTIC ULCER

It can safely be stated without fear of contradiction that the cause of gastroduodenal ulcer is unknown. The subject is one which has attracted great interest on the part of clinicians, physiologists and experimentalists and the constantly increasing volume of literature on the etiology of peptic ulcer attests to the fact that no one theory has been validated to the exclusion of others. A large part of this literature has been reviewed in admirable fashion by McCann (1929)²³⁸, De Bakey (1937)²³⁹, Linn (1945)²⁴⁰ and many others. Certain facts are known concerning the incidence of peptic ulcer which have never been adequately explained. Some of these are the increased susceptibility of the male²⁴¹ the fact that in certain families there seems to be a predisposition

toward ulcer,³⁰⁰ the fact that peptic ulcer is extremely rare in conjunction with either diabetes or pregnancy, the idea that certain constitutional types have a predisposition toward ulceration,³¹¹ and the fact that ulcer is extremely rare as a spontaneous occurrence in lower animal forms³¹¹ although so common in man.

Nevertheless, as a result of a great variety of clinical and experimental research a considerable number of factors are thought to play a greater or lesser part in the pathogenesis of peptic ulcer, some of the more important factors will be briefly considered. The factor which has achieved the greatest prominence especially with regard to ulcer therapy, is the chemical or acid peptic factor.

The Acid Peptic Factor

Peptic ulcer occurs only in those parts of the gastrointestinal tract which are bathed by acid gastric juice.³¹² In addition to the stomach and duodenum it may occur in or adjacent to areas of heterotopic gastric mucosa which is sometimes found in the lower esophagus or in a Meckel's diverticulum³¹³ or it may occur in lower intestinal segments if they are brought into contact with the acid gastric juice. As Rivers (1934)⁴¹⁷ stated, "When tissues other than those naturally accustomed to the chemical and mechanical action of gastric juice are exposed to the aggression of acid chyme the potentiality for ulceration promptly develops."

The Digestive Power of Gastric Juice—When the known property of pepsin and hydrochloric acid to digest living tissue is considered, it is really surprising that peptic ulcer is not a universal occurrence. John Hunter felt that the "living principle" prevented digestion by gastric juice but this was refuted by the classic experiment of Claude Bernard who immersed the leg of a living frog in the gastric fistula of a dog and obtained digestion of the leg. It is interesting to note that early in his career Dragstedt (1917)⁴¹⁷ came to the conclusion that the digestive action of gastric juice was not important in ulcer genesis. Bernard's experiment has since been confirmed by Dragstedt and Vaughan (1924)⁴²⁵ both *in vitro* and *in vivo*. In addition in dogs these workers implanted various organs (spleen, kidney, segments of bowel) with blood supply intact into the anterior wall of the stomach and found that not only were the organs not digested but in some cases the implanted organ was covered over by a layer of regenerated tall columnar gastric epithelium. The remarkable regenerative capacity of the gastric mucosa has been demonstrated by Ferguson (1928)⁴²¹ who found that large artificially produced defects would heal. It has recently been demonstrated⁴⁰ that a hypersecretion of acid gastric juice induced by repeated injections of histamine in human will seriously interfere with this process of repair. Katzenstein (1913)⁴² found that of various organs implanted into the stomach only the mucosa of the stomach and duodenum were resistant to the digestive action of gastric juice. However organs implanted in the duodenum in a more alkaline medium are not digested.⁴¹ Price and Lee (1946-1947)^{400, 40} implanted a great variety of organs more deeply into the lumen of the stomach than Dragstedt and Vaughan and found that all of these organs were digested but once they were covered over by regenerated gastric mucosa no further digestion occurred. This digestive process

was accelerated by hypersecretion produced by histamine in beeswax to such an extent that the gastric mucosa itself was digested.

If the stomach of an experimental animal is isolated, with blood supply and vagal innervation intact and the exit of the juice secreted is prevented for a time Dragstedt (1935)¹¹⁴ has shown that the gastric mucosa itself will be digested with the formation of chronic perforating ulcers. Similar results have been obtained by Stein, Grossman, and Ivy (1947)¹⁶⁴ with closed Heidenhain (denervated) pouches.

The Role of the Pylorus.—Physiologists agree that a true hyperacidity in the sense of secretion of hydrochloric acid at increased concentration does not occur, but that an apparent hyperacidity may be the result of a hypersecretion of juice of normal acidity or a normal rate of secretion with interference with emptying of the stomach and interference with regurgitation of alkaline duodenal contents.²⁸ It is natural, therefore that a great deal of interest should center on the role of the pylorus in gastroduodenal ulcer. Hughson (1927)¹²³ noted that ulcers produced by excising segments of mucosa remained active twice as long in animals with normal pyloric function as in those in which the pylorus had been defunctionalized by sectioning the circular muscle. Acute ulcers produced by the submucosal injection of 5 per cent silver nitrate as reported by Friedman and Hamburger (1914)¹⁶⁴ became chronic only in those animals in which partial pyloric obstruction had been produced. In these animals there was an increase in the acidity of the gastric contents. Elman and Eckert (1933)¹⁵⁶ partially closed the pylorus in dogs with a ligature; one dog developed a perforated duodenal ulcer the remainder showing a marked duodenitis. The disturbance in the normal acid-alkali relationship produced by partial pyloric stenosis contrived by wrapping a collar of jejunal muscle with intact nerve supply around the pylorus was reported by Morton (1934)¹⁷⁶ to cause a duodenitis similar to that seen clinically associated with duodenal ulcer in each animal studied. In acute experiments Shay's group (1945)¹²² produced ulcers in the rumen of rats by the simple expedient of ligating the pylorus. These ulcers which occurred seventeen to nineteen hours after operation were attributed to the presence of a large amount of unbuffered gastric juice. It has been shown¹²⁸ that in patients with active peptic ulcer the neutralization of an acid test meal is slower than normal. Histologic evidence that the pylorus plays an important role in ulcer production was presented by Truesdale (1915)⁴² who found that resected specimens from patients with active ulcer showed a hypertrophy of the pyloric musculature.

'Hyperacidity' and Peptic Ulcer.—It is commonly thought that a high acid secretion is the usual accompaniment of benign gastric or duodenal ulcer. In some 2500 cases of benign ulcer Palmer (1942)³⁹ failed to find a single one that had true acidity to histamine. Studies of the gastric acidity in large series of cases such as those of Friedenwald (1912)¹⁶⁰ Emery and Monroe (1929)¹⁴¹ Heintz and Welker (1925)¹¹³ and Palmer (1942)³⁹ have shown that a patient with benign ulcer may have almost any degree of acidity but will always secrete some acid. Palmer (1947)¹⁶⁶ found that normal or subnormal

acid was more the rule than the exception in cases of gastric ulcer although patients with duodenal ulcer usually had a high acid concentration. Vauvart and co workers (1936)⁴⁶⁹ noted that not only the acidity but the pepsin concentration of gastric secretion was higher in most cases of duodenal ulcer than in those cases with gastric ulcer.

While most writers feel that an ulcer may result from a hypersecretion of acid juice, there is a certain amount of experimental evidence to suggest that such a 'hyperacidity' is a result, rather than a cause of the ulcer. Dragstedt and Vaughan (1924)¹² produced chronic ulcers by injecting silver nitrate beneath the mucosa of dogs' stomachs, and noted that gastric acidity rose after development of the ulcers. A similar occurrence has been observed by Cheney (1938)⁸⁷ after the production of gastric ulcers in chicks by feeding a deficient diet. Such observations may be explained on a basis of pylorospasm secondary to ulcer. Harper (1932-1935)^{207, 208} connected closed gastric pouches of dogs to the body surface by interposing loops of small bowel with blood supply intact, arranged in an antiperistaltic fashion. Ulcers many of which perforated developed in these loops of bowel, since the peristalsis of the bowel prevented egress of the gastric secretion, and on studying the acid content of the pouches it was found that as the ulcers developed the acidity rose, but not before. However in those preparations in which a pyloric pouch was utilized, and in which no acid secretion occurred no ulcers developed.

This problem has been attacked in a different fashion, by studying the reaction of the duodenal contents. The reaction of the isolated duodenum in the dog is quite constant,^{2, 3} with an alkalinity of pH 7.10 to 8.15. However Mann and Bollman (1935),³ characterizing the duodenum as the 'chemical battle ground of the gastrointestinal tract' have observed that the reactions of the intact duodenum in continuity with the rest of the gastrointestinal tract may fluctuate remarkably. When highly acid values were found in the stomach of dogs equipped with Mann fistulas the duodenal content was also found to be acid although normally it was just on the alkaline side of neutrality.²²³ Stevens (1935)⁴⁶⁹ demonstrated the capacity of the duodenum to neutralize buffer and dilute acid solutions perfused through it. Thomas and his co workers (1940, 1942)^{5, 4} cannulating various portions of the gastrointestinal tract in dogs found that at the height of the acid secretory curve in the digestive process the pH of the duodenal contents was rarely less than 3.0 and usually nearer 4.0.

A comparison made between the duodenal contents of relatively normal patients and of patients with peptic ulcer by Morton (1929)^{3, 2} using two tubes the position of which was checked by x-ray examination showed that there was no free hydrochloric acid in the duodenal contents in the ulcer free patients but free hydrochloric acid was found in the duodenal contents of those with peptic ulcer. This was attributed to a disturbance in pyloric function interfering with neutralization. Corresponding studies and comparisons were made by Berk, Rehfuess and Thomas (1942)^{87, 88}. Although free acid was usually absent in the duodenal contents they felt its presence was not abnormal. They observed that in the normal subject the duodenal bulb is endowed with a ca

capacity to dilute, buffer and neutralize gastric chyme that generally exceeds the physiologic needs, the average pH varying between 5.0 and 5.6, but in patients with duodenal ulcer this neutralizing ability is impaired although not wholly lost. This particular subject has recently been reviewed by Comfort (1945),²³ who concluded that the reaction of the duodenal contents in the fasting normal individual is probably alkaline although it becomes more acid each time the stomach empties, but the reaction of the duodenal contents in patients with duodenal ulcer is more acid both fasting and during digestive secretion.

Experimental Ulcer Production by Disturbance of Acid-Alkali Relation ship—

Administration of acid. In 1893 Matthes³ resected segments of small bowel with the blood supply maintained closed one end, and bringing the open end out on the abdominal wall was able consistently to produce necrosis and perforation by irrigation with a mixture of pepsin and hydrochloric acid. He studied the resistance of various tissues to digestion by gastric juice and found that the gastric mucosa was most resistant of all but his conclusion is yet not invalidated was that hydrochloric acid in sufficient concentration over a long enough period of time could produce necrosis of any tissue and after necrosis occurred enzymatic digestion of the tissue could proceed. Recently Kolouch (1941)² has employed a similar method in studying the digestive effect of the constituents of gastric juice on various segments of bowel. Gallagher (1928)¹⁰ produced gastritis, duodenitis and acute ulcers in dogs to which he administered dilute HCl through a tube twice daily but was unable to produce chronic ulcers. However after about four weeks of instilling 0.4 per cent HCl through a gastric fistula for eight hours each day Mann and Bollman (1932)²²⁰ were able to produce chronic ulcers on the lesser curvature of the stomach. Friedenwald, Feldman and Morrison (1933)¹ injected various substances into the muscularis of the dog's stomach; they found that weak solutions of hydrochloric acid had no effect but stronger solutions produced definite ulceration. Acute shallow ulcers of the stomach and duodenum were produced by Ochsner (1932) and Hosoi (1934-1936)^{17, 234} by feeding dogs 1 per cent HCl. In none of these experiments were the ulcers produced analogous to the typical peptic ulcers of man although the experiments did demonstrate the corrosive action of hydrochloric acid. The importance of pepsin in conjunction with hydrochloric acid has been stressed by Matzner and Windwer (1937)²² and by Schiffman and Warren (1942)¹ who perfused the stomach and various segments of bowel with acid with or without pepsin. Ulcer production was at a maximum when pepsin was added to the solution. The optimum pH for acid-peptic digestion was found to be 1.1 to 1.3. The recent studies of Foellmann's (1949)¹⁸ group indicate that the acidosis accompanying intra-gastric perfusion of acid-pepsin mixtures is important in the development of ulceration.

Deviation of duodenal contents. In 1909 Bickel² removed the duodenum in two dogs transplanting the common bile and pancreatic ducts onto the abdominal wall and performing a gastrojejunostomy. One dog survived only 10 days but the other dog surviving 41 weeks developed two large and two small

ulcers in the neighborhood of the anastomosis and, in addition, a large perforated ulcer in the jejunum 8 cm distal to the anastomosis. Bickel felt that this was convincing demonstration of the importance of pancreatic, duodenal, and biliary secretions in the prevention of digestion of the intestine by acid chyme. Further proof was added by Baggio (1924)² who performed Roux en Y gastrojejunostomies on dogs either in conjunction with pyloric exclusion or resection of the pyloric portion of the stomach so that the alkaline duodenal secretions entered the jejunum at a considerable distance from the gastrojejunal anastomosis. A substantial number of dogs surviving these procedures developed jejunal ulcers distal to the gastrojejunal anastomosis. Jejunal ulcers had previously been produced by Exalto (1911)¹⁴ as a result of Roux en Y gastrojejunostomies in conjunction with feeding hydrochloric acid. Another type of procedure in which a pyloric exclusion was done, the duodenum severed at its distal end, the stomach anastomosed to the proximal jejunum and the terminal end of the duodenum anastomosed to the cecum, was also done by Exalto. Each of three dogs developed a jejunal ulcer. Denk (1921)¹⁰⁰ was able to demonstrate two jejunal ulcers in a dog in which the pylorus had been resected, the jejunum divided 25 cm from the pylorus, the aboral end being employed to make a gastrojejunostomy, and the oral end anastomosed to the terminal ileum so as to direct the duodenal contents to the terminal ileum. This procedure was supplemented by feeding the dog dilute hydrochloric acid.

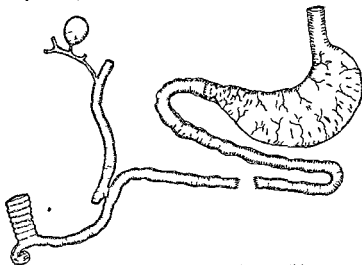


Fig 3—Mann-Williamson operation (diagrammatic)

The second experimental procedure of Exalto was slightly modified twelve years later by Mann and Williamson (1923)²² who sectioned the duodenum just below the pylorus, did an end to end gastrojejunostomy and anastomosed the distal end of the duodenum to the terminal ileum. Such an operation which has come to be called the Mann-Williamson procedure in this country will produce jejunal ulcers in 90 to 100 per cent of animals (Fig 3).

This work has been confirmed abundantly by the work of Morton (1927),^{30, 31} Weiss and Gurriaran (1929),³²¹ Weiss and Hubster (1931),³²² Owings and Smith (1932),³²³ Orndorff, Fraley, and Ivy (1936),³²¹ and many others. These ulcers developed ten days to three months after the operative procedure,^{32 323} usually occurred just distal to the site of gastrojejunal anastomosis, were of the chronic variety, and were thought to be analogous to the peptic ulcers of human beings in every respect except as to location. Ivy (1946)²⁴⁵ felt that they were entirely analogous to the postoperative jejunal ulcer occurring in human beings after gastroenterostomy or gastric resection.

In any case such a procedure has proved to be of inestimable value in the experimental study of the pathogenesis and therapy of peptic ulcer. Owings and Smith (1932)³²³ showed that if when ulcers developed in Mann-Williamson dogs the enterointerostomy was taken down and the distal end of the duodenum anastomosed to the stomach, some of the ulcers would heal as a result of the return of the alkaline duodenal secretions. An increased acidity of gastric contents following the Mann-Williamson procedure has been shown by Wilhelmj and Finegan (1938)²⁵ who noted that the acidity continued to rise after a test meal and the usual abrupt terminal decrease in acidity failed to occur. A marked increase in the intestinal phase of gastric secretion and in the continuous secretion after the Mann-Williamson operation was recorded by Ivy's group (1936)³²¹ who thought the ulceration was due to the deleterious action of such an unbuffered secretion on the especially susceptible jejunal mucosa. Recently they have shown^{18 344} that the lowering of acid secretion by the administration of enterogastrone prevented ulcer formation in a sizable proportion of a series of Mann-Williamson dogs. In the hands of Saltzstein and his co-workers (1947)⁴³³ however, enterogastrone prevented ulcer development in only 20 per cent of their Mann-Williamson dogs.

Various other experimental procedures have reproduced situations which, in effect, are analogous to a Meckel's diverticulum in which secreting gastric mucosa is found adjacent to susceptible intestinal mucosa at a considerable distance from the alkaline secretions of the duodenum. Thus Winkelbauer and Starlinger (1928)³⁴¹ produced jejunal ulcers in dogs by performing a pyloric exclusion operation accompanied by gastrojejunostomy and an enteroenterostomy at a considerable distance from the gastrojejunostomy. Matthews and Dragstedt (1932)³⁴⁴ anastomosed Pylorol gastric pouches to the terminal ileum and produced ulcers in the ileum just distal to the anastomosis. The anastomosis of Pylorol or Heidenham pouches to the jejunum was shown by Ochsner, Gage, and Hosoi (1934-1936)^{14 344} to result in jejunal ulcer formation; these ulcers were prevented in a high percentage of dogs by directing the gall bladder bile to the gastric pouch.

Numerous attempts have been made to determine experimentally the relative importance in the protective process of dilution, neutralization, and buffering of the bile, pancreatic juice, and succus entericus.

¹ The Role of the Succus Entericus in Neutralization. Comparatively little work has been done in evaluating the importance of the duodenal secretion

ulcers in the neighborhood of the anastomosis and, in addition a large perforated ulcer in the jejunum 8 cm distal to the anastomosis. Bickel felt that this was convincing demonstration of the importance of pancreatic duodenal and biliary secretions in the prevention of digestion of the intestine by acid chyme. Further proof was added by Baglio (1924)²² who performed Roux en Y gastrojejunostomies on dogs either in conjunction with pyloric exclusion or resection of the pyloric portion of the stomach so that the alkaline duodenal secretions entered the jejunum at a considerable distance from the gastroduodenal anastomosis. A substantial number of dogs surviving these procedures developed jejunal ulcers distal to the gastrojejunal anastomosis. Jejunal ulcers had previously been produced by Exalto (1911),¹⁴ as a result of Roux en Y gastrojejunostomies in conjunction with feeding hydrochloric acid. Another type of procedure in which a pyloric exclusion was done, the duodenum severed at its distal end, the stomach anastomosed to the proximal jejunum and the terminal end of the duodenum anastomosed to the cecum was also done by Exalto. Each of three dogs developed a jejunal ulcer. Denk (1921)¹⁰⁰ was able to demonstrate two jejunal ulcers in a dog in which the pylorus had been resected, the jejunum divided 25 cm from the pylorus the aboral end being employed to make a gastrojejunostomy and the oral end anastomosed to the terminal ileum so as to direct the duodenal contents to the terminal ileum. This procedure was supplemented by feeding the dog dilute hydrochloric acid.

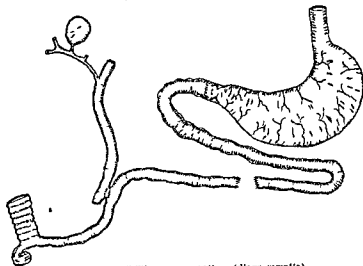


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has come to be called the Mann-Williamson operation. It produces jejunal ulcers in 90 to 100 per cent of animals (Fig 3)

Obstructive jaundice produced by ligation and division of the common duct as reported by Bollman and Mann (1932),² resulted in the development of acute subacute, or chronic ulcers of the duodenum or stomach in 64 of 87 dogs. It is interesting to note that the development of ulceration could not be prevented by the oral administration of gall bladder bile twice daily. Ivy, Schrager, and Morgan (1932)¹³³ noted gastric or duodenal ulcers in 5 of 7 dogs with chronic icterus and hepatitis resulting from plastic procedures on the common duct. Duodenal ulcers were demonstrated by Blank (1935)⁴⁵ in dogs with external biliary fistulas but when such dogs were fed back the collected bile, they did not develop ulcers. Blank's series of dogs was quite small detracting somewhat from the significance of this work.

Using a fistula of the Mann type, McRoberts (1935)³⁴ studied the reaction of the duodenal content before and after the exclusion of bile from the duodenum by means of a biliary fistula. He found no significant alteration in the pH after bile was prevented from entering the intestine. Recently by exposing the intestinal loops of dogs to various acid pepsin mixtures both with and without the addition of bile salts, Driver and Carmichael (1945)¹³⁶ found that the digestive action of the pepsin on the intestinal mucosa was markedly inhibited by the presence of bile salts at a pH of 1.25.

The Role of the Pancreatic Juice in Neutralization. Olek (1928)³ as a result of his studies on regurgitation of duodenal contents in dogs came to the conclusion that the most important factor in the reduction of gastric acidity was the pancreatic juice. The pancreatic ducts of dogs were ligated by Yesko (1928)⁵⁴ with only a slight resulting increase in the gastric acidity. Yesko made no mention of ulcer formation but no protocols of individual dogs were included in his report. Elman and McCaughan (1927-1928)¹³⁴ ¹³⁵ ligated the minor pancreatic duct established a pancreatic fistula via the major pancreatic duct performed a cholecystostomy and by means of a series of tubes and clamps established a system whereby it will they could either cause the exit of the entire external pancreatic secretion or cause the return of that secretion to the duodenum via the gall bladder and common duct. Dogs in which the pancreatic juice was withdrawn developed signs of gastric irritability, vomiting and asthenia and the gastric contents were found to contain a higher free and total acidity than normal but when pancreatic secretion was then allowed to enter the duodenum these dogs came to life and the acid values declined to normal. Elman and Hartmann (1931)¹³³ ¹³² showed that if these dogs were deprived of their external pancreatic secretion for two weeks or longer even though they were kept in relatively good condition by the administration of intravenous fluids the dogs developed duodenal ulcers just distal to the pylorus. However, Berg and Zucker (1932-1934)³⁶ ³⁷ recorded that of fourteen dogs maintained with a pancreatic fistula for fourteen to forty days only one dog developed (duodenal) ulceration and this dog showed evidence of obstructive jaundice. Moreover five dogs with ligation of the pancreatic ducts showed no changes at all in their stomachs and duodenums. Berg felt the pancreatic juice was quite unimportant as a factor in protection of the mucosa from ulceration.

alone, as a neutralizing force protecting the intestine from the acid chyme. Grev (1919)¹⁹¹ attempted a duodenectomy in dogs in three stages. After completion of the first two stages, which consisted of division of the common duct with cholecystojejunostomy, and transplantation of the major pancreatic duct to the jejunum with ligation of the accessory pancreatic duct two of his dogs developed perforated jejunal ulcers. Another dog failed to survive the third stage (duodenectomy) and the only surviving dog died in 9½ months with intestinal obstruction from adhesions but no evidence of ulcer. This demonstrated that the duodenum was not essential for life. Shortly afterward Minn and Kawamura (1922)¹⁹² carried out similar procedures on a series of dogs and other animals implanting the common bile and pancreatic ducts into the jejunum just distal to the gastrojejunal anastomosis. Two of ten dogs developed jejunal ulcers just distal to the suture line.

The Role of Bile in Neutralization The importance of bile as a neutralizing and protective agent has received enough stress so that Bogoras (1925)¹⁹³ was led to advocate cholecystogastrostomy as a therapeutic measure for gastric ulcer. He reported that the free acidity of patients so treated declined after operation. More recently Bergh (1938)¹⁹⁴ recommended the administration of bile salts as an adjuvant in the treatment of peptic ulcer, the rapid evidence of ulcer healing noted in a large proportion of cases with this form of therapy was ascribed to a stimulation of the further flow of bile by the bile salts.

Various observers¹⁹⁵⁻¹⁹⁶ have noted that in experimental animals the pH of the liver bile is between 7.07 and 8.55 definitely on the alkaline side. However, the same observers recorded an acid pH for gall bladder bile varying from 5.18 to 7.47. Neilson and Meyer (1921)¹⁹⁷ made similar observations in experimental animals, but in studies on a patient with a bile fistula they found the pH to be 8.0, while gall bladder bile had a pH varying from 7.7 to 8.6. These observations should cast some doubt on the neutralizing power of the bile as delivered to the duodenum. nevertheless a large amount of work has been done to

Smith

had a

Hooper

and Whipple (1916)¹⁹⁸ found that deviation of the bile from the gastrointestinal tract produced by ligation of the common duct with cholecystostomy resulted in intestinal disorders accompanied by melena in all the dogs so treated and one dog died with a large duodenal ulcer. At a later date the same group (1935)¹⁹⁹ reported duodenal ulcers in 9 of 33 dogs prepared in this manner. Of 43 dogs in which the gall bladder had been implanted into the lumbar pelvis with ligation of the common duct Kapsinow (1926)²⁰⁰ found duodenal ulcers in 17, these ulcers usually occurred in the neighborhood of the ampulla of Vater. Berg, Johnston and Jobling (1927)²⁰¹ found duodenal or gastric ulcers in 7 of 9 dogs in which biliary fistula had been fashioned and (1930)²⁰² in 9 of 16 dogs with obstructive jaundice. Weiss and Hubster (1931)²⁰³ were unable to produce ulcers in dogs by deviating the bile to the terminal ileum but those dogs did develop an acute inflammation of the duodenum and antrum which the authors thought to be a "pre ulcer stage."

Kehrer (1914)²⁴⁴ was able to demonstrate three dogs with deep chronic ulcers and three with acute erosions out of fifteen dogs in which he had divided the common duct as well as the pancreatic ducts anastomosing the gall bladder and major pancreatic duct to the ileum. This seemed to indicate that the duodenal juice had little protective value but the experiments of Bauer and Aron (1933)²⁴⁵ seemed to indicate that the duodenal juice was of prime importance. Unfortunately these experiments were done only on one dog. This dog failed to develop ulceration after resection of the head and body of the pancreas or even after division of the common duct and cholecystoenterostomy at a second stage. However following a third stage operation, in which the duodenum was resected and continuity reestablished by a gastrojejunostomy, the dog died in nineteen days with three jejunal ulcers in the neighborhood of the anastomosis. Mann and Williamson (1923)²²⁹ produced jejunal ulcers in only two of ten dogs in which the duodenum had been extirpated with reimplantation of the pancreatic and bile ducts in the neighborhood of the gastrojejunal anastomosis and in ten of thirty one dogs in which the bile and pancreatic ducts were transplanted to the terminal ileum but when all three types of secretion were deviated to the terminal ileum nearly all the dogs developed jejunal ulcer.

The suggestion that bile was the most important of the three factors in neutralization was advanced by Owings and Smith (1932)²³⁴ on the basis of their experiments. Of five dogs in which the common duct was divided and cholecystoenterostomy done eighteen inches below the ligament of Treitz two developed duodenal ulcers while these workers were unable to demonstrate ulcers following section of the pancreatic ducts and transplantation of the main pancreatic duct to the jejunum eighteen inches below the ligament of Treitz in another series of dogs. Strangely enough when the procedure in this second series of dogs was supplemented by ligation of the common duct and cholecystoenterostomy (close to the site of anastomosis of the pancreatic duct) the dogs still failed to develop ulcer. This seems to indicate that the succus entericus is of some importance after all.

Graves (1931)²²² was unable consistently to produce ulcers either by the deviation of pancreatic juice or of bile to the terminal jejunum but when he added to these procedures a modified Mann-Williamson operation sectioning the jejunum above the site of transplant of the pancreatic or common bile duct he found that ulcers developed near the anastomosis whether it was theoretically protected either by bile or pancreatic juice. However he observed that the ulcers that occurred in the jejunum protected by pancreatic juice were not so large and not so often multiple as those occurring in the jejunum protected by bile so he attributed more importance to the pancreatic juice.

A comparative study was made by DeBakey (1937)²⁴⁶ in which curiously all his procedures were done in conjunction with pyloric occlusion and anterior (short loop) gastrojejunostomy in operation which itself is known to favor the development of jejunal ulcer. With this procedure alone 10 (50 per cent) of 20 dogs developed jejunal ulcer with deviation of the pancreatic juice to the terminal ileum added to this procedure 7 (70 per cent) of 10 dogs developed

✓ This problem has been studied rather thoroughly by Hoerner (1935)²² in a series of experiments. Using a Mann type of fistula to the duodenum he found that when the pancreatic ducts were excluded the total buffer secretions in the duodenum diminished but the remaining bile and succus entericus were capable of maintaining the normal reaction of the duodenal content except just after the entrance of gastric juice of high acidity. Studying dogs with pancreatic fistulas, he found the duodenal content slightly more acid, and it is significant that 42 per cent of these animals developed peptic ulcer. The pancreatic secretion was always all time in reaction but its buffering capacity was found to vary considerably reaching a maximum one to three hours after the ingestion of food, and diminishing as the acidity of the duodenal content decreased. At its maximum buffering capacity 1 cc of pancreatic secretion was capable of neutralizing an equal quantity of N/10 hydrochloric acid. It is peculiar that the dogs in which the pancreatic ducts were excluded did not develop ulcer. Dringstedt (1943)¹⁰ has also observed that although nearly 100 per cent of dogs with pancreatic fistulas develop gastric or duodenal ulcer and 33 per cent of dogs with ligated pancreatic ducts develop ulcer in over 440 dogs in which the pancreas was removed entirely gastric or duodenal ulcer was found less than a dozen times. No adequate explanation for this phenomenon has as yet been advanced and an experimental solution would contribute greatly to physiologic knowledge. Manhoff and Poth (1947)²²⁰ recently found that ulcer formation and perforation occurred unusually rapidly with the administration of histamine in beeswax to dogs that had been pancreatectomized or in which the pancreatic ducts had been ligated.

✗ An interesting clinical observation which to some extent corroborates this experimental evidence was cited by Morton and Graham (1930)²³. They recorded the case of a woman who had had a cholecystectomy and choledochostomy. After removal of the T tube from the common duct during the postoperative period she became quite ill vomited changed blood and died. Autopsy showed a large stone apparently missed at operation obstructing the common duct and another stone obstructing the pancreatic duct the immediate cause of death was a large posterior wall duodenal ulcer which had eroded into the pancreas and caused the fatal hematemesis. There had been no evidence of this ulcer at the time of operation and it was felt that the ulcer formation was a result of interference with the discharge of alkaline bile and pancreatic juice into the duodenum.

✓ Attempts to Assess the Relative Protective Value of Bile Succus Entericus and Pancreatic Juice. The buffer value of bile and pancreatic juice has been compared in vitro by titration with hydrochloric acid by Jones (1931)²⁴. No great difference was found between the two and he found that they were more or less compensatory for when the buffer capacity of one decreased that of the other increased. It should be stated that Jones studied bile obtained from the common duct of an animal that had been cholecystectomized it has already been noted that hepatic bile is much more alkaline than gall bladder bile.

his associates (1932),³⁰ although modified by using a short duodenal loop anastomosed to the antrum instead of to the fundus. By thus making the duodenal contents immediately available for protection of the jejunal mucosa they were able to prevent the development of jejunal ulcer in all fourteen of their dogs. The importance of neutralization at the stoma was also emphasized by the work of Maier and Grossman (1935)³¹ who felt that in the Schmilschky procedure and its variants some of the alkaline duodenal content is lost for effective neutralization at the stoma and the procedure is therefore less valuable than an ordinary gastrojejunostomy.

Wangensteen (1940-1942)³⁰¹⁻³¹² gave the Schmilschky procedure a clinical trial in three cases of gastrojejunal ulcer. One of these patients died with a perforated new marginal ulcer, the second died with a gross hemorrhage from a gastric ulcer and the third did not show much decrease in acidity of secretion and maintained a prolonged emptying time. The experimental evidence at hand indicates that there is no rational basis for the clinical use of such an operation.

Ulcer Production By Histamine—The known property of histamine to evoke a highly acid gastric secretion has stimulated numerous attempts to produce ulcers experimentally by histamine injection. Buehner and Molloy (1927)⁴⁰ and Burke de la Camp (1929)⁴¹ were able to produce acute but not chronic ulcers in the forestomach of rats by repeated subcutaneous injections of histamine. In the hands of O'Shaughnessy (1931)⁴² this method failed with cats but hemorrhagic areas and acute ulcers were produced by injecting histamine directly into the muscularis of the stomach of these animals. Chronic ulcers were finally produced in the forestomachs of rats although not consistently by Harde (1932)⁴³ by repeated subcutaneous administration of histamine. Flood and Howes (1934)¹³⁸ found that artificial defects created in the mucosa of the stomachs of cats and dogs healed completely in two weeks, but when histamine was administered parenterally twice daily to these animals the healing process was considerably delayed. Extension of artificially produced mucosal defects with histamine administration was noted by McIlroy (1927)³⁴⁴. Orndorff, Bergh and Ivy (1933)³⁰⁰ attempted to maintain a hypersecretion in dogs by injecting every two hours either histamine (producing a juice rich in acid) pepsin (producing a juice rich in pepsin) or a combination of these drugs but they were unable to produce ulcers in these dogs.

It remained for Walpole, Varco, Code, Hay and Wangenstein (1940-1942)^{42, 43, 44, 45} to determine a suitable vehicle (beeswax and mineral oil) for the histamine so that by a single injection each day a hypersecretion could be maintained over a twenty-four hour period. The prolonged action of this acid gastric juice resulted consistently in the development of subacute or chronic frequently perforating ulcers in the stomachs and duodenum of dogs, guinea pigs, cats, chickens, ducks, woodchucks, calves, monkeys, rabbits and swine. Ulcer production in the latter animal is of especial interest since the stomach of the pig is more like that of man than the stomach of any other animal. Curiously enough administration of an antihistamine substance, Benadryl, in conjunction with the histamine in beeswax failed to alter the gastric secretory

jejunal ulcer, with deviation of bile to the terminal ileum accompanied by pyloric occlusion and gastrojejunostomy, 15 (90 per cent) of 20 dogs developed jejunal ulcer, and in a series of 10 dogs in which all these procedures were done, all of the dogs developed jejunal ulcer. Thus, he concluded that bile was the most important, pancreatic juice less important, and the succus entericus the least important as a means of neutralizing the gastric acid and preventing ulcer formation.

Bachrach, Schmidt, and Beazell (1939)²⁷ attached some importance to the bile. In a series of 19 dogs with the pancreas separated from the duodenum only 1 dog developed a duodenal ulcer. Perforated duodenal ulcers developed in 2 dogs with biliary fistulas in which the bile was fed back through a long tube passing through the common duct into the bowel and terminating 50 cm below the ampulla of Vater but 13 other dogs in which the bile was returned into the duodenum failed to develop ulcer.

Total Intragastric Regurgitation of Alkaline Duodenal Contents—With such a weight of evidence, albeit somewhat conflicting evidence, that the succus entericus, bile and pancreatic juice are important in protecting the gastric and duodenal mucosa from the digestive action of the gastric juice, it would seem reasonable to suppose that by emptying some or all of these secretions directly into the stomach, the gastric acidity might be reduced sufficiently to ablate the ulcer diathesis. Schmilinsky (1918)⁴⁴ advocated as a mode of surgical therapy for ulcer a procedure which had been tried in dogs by Chlumsky⁴⁵ in 1900. This consisted essentially of a von Eiselsberg pyloric occlusion combined with resection of the proximal jejunum, the oral end of which was anastomosed to the fundus of the stomach while the aboral end was anastomosed to the stomach in the region of the antrum. Although he noted that the gastric acid values were quite high during digestion after this procedure, Schmilinsky reported cures in five patients with duodenal ulcers and three patients with jejunal ulcer.

The effects of deviation of the pancreatic juice or bile into the stomachs of dogs on the acidity of gastric secretion were studied by Grey (1916, 1917)^{239, 250}. He reported that cholecystogastrostomy had no appreciable effect on the acidity of the gastric contents but that the presence of pancreatic juice in the stomach as shown by trypsin determinations actually led to a moderate increase in acidity in the late phase of the digestive process, which was attributed to compensatory activity of the gastric glands. It has since been shown²⁶ that alkali is an effective stimulus of gastric secretion.

Schmilinsky's procedure was repeated in dogs by Keppich (1921)⁶⁰ with the resultant development of jejunal ulcers but when a resection of the pyloric antrum or a hemigastrectomy was added to this procedure no ulcer developed. The same procedure, with the variant of making an end-to-end anastomosis between the pyloric end of the stomach and the aboral end of the jejunum was repeated by McCann (1929)²³⁸ who reported that 80 per cent of his dogs developed jejunal ulcers. He found the essential character of the acid secretory curve unchanged after such an operation but the acidity rose at the time of ulcer development. McCann's procedure in turn was repeated by Weiss and

Mucosal defects produced by snipping out areas of mucosa took longer to heal on the lesser curvature and in the antral region than in other areas, and when such defects were produced in conjunction with the Mann-Williamson procedure only those defects on the lesser curvature became chronic ulcers. Like wise when patches of jejunum were implanted in the stomach of dogs then subjected to the Mann-Williamson procedure only those patches in the lesser curvature region exhibited ulcers. Concerning two of the ulcers in McCann's (1929)³³⁹ dogs which had a modified Schmilinsky procedure performed, numerous dog hairs were found embedded in the base of one and the other, which was performed had a piece of turnip protruding through it. The force required to embed these objects was attributed to the 'jet effect'.

Jenkins and Palmer (1931)³⁴⁰ attempted to eliminate the mechanical factor by varying the Mann-Williamson procedure, making an unusually wide stoma side to side gastroenterostomy instead of the usual end to end anastomosis but were unable to show any difference in the incidence of ulcer in their dogs. The consistency of the diet as a traumatic factor was emphasized by the work of Fauley and Ivy (1930)³⁴¹. Defects in the gastric mucosa produced by excising small portions healed irrespective of the diet administered, but if nonabsorbable material was sutured in the base of the defect chronic ulcers developed if the dogs were fed a rough diet while the defects healed if a bland diet was administered. Driver, Chappell and Carmichael (1945)³⁴² furnished further proof of the importance of Mann's 'jet effect'. Exposing loops of dogs in testines to 0.1 per cent pepsin in N/10 HCl under various hydrostatic pressures, they found that a rise in intraintestinal pressure resulted in a marked increase in the extent of peptic digestion leading to perforation in a shorter time. In controls exposed to saline alone under the same pressures no necrosis occurred.

Diminished Tissue Resistance to Acid-Peptic Digestion

The Vascular Factor—For many years pathologists have observed that sclerosis or thrombosis of small arteries is frequently seen in resected or autopsy specimens of peptic ulcer. This has led some to believe that ulcer formation is in part due to localized areas of anemia actual necrosis from loss of blood supply or some type of embolic phenomenon. Indeed ulcers have been produced experimentally in the stomach of the rat³⁴³ by vascular ligation but it has already been noted that the stomachs of man and dogs have a different anatomic arrangement of the blood supply and in fact obliteration of the greater portion of the blood supply in the dog's stomach results in no great change in the mucosa.³⁴⁴ Baronofsky and Winessteen (1945)³⁴⁵ however have been able to produce gastric and duodenal ulcers many of which perforated in various types of experimental animals by provoking chronic arterial spasm through the parenteral administration (in beeswax) of such vasospastic substances as Pitressin and epinephrine.

The Minnesota group also became interested in the fact that peptic ulcer or hematemesis occasionally occurred as a complication of fractures³⁴⁶ and were able to demonstrate in a variety of animals that fracture of the long bones curettement of the bone marrow³⁴⁷ or actual intravenous injection of normal

response or to prevent the formation of ulcers,¹⁸ and the administration of antero-gastron¹⁹ likewise failed to prevent the formation of histamine induced ulcers.^{19a}

¶ The acid peptic factor in ulcer production and the relative protective value of various neutralizing secretions have been discussed in considerable detail because of the importance of this factor in connection with ulcer surgery. It is, however, obvious that this is not the only factor concerned in the causation of peptic ulcer. More than forty years ago MacCallum (1904)^{21a} wrote "It may be said that gastric ulcers may be produced by anything which causes necrosis of the mucosa of the stomach, and thus subjects it to the digestive action of gastric juice." This observation to a greater or lesser extent, still holds good today. A number of other factors concerned in the etiology of peptic ulcer will be discussed more briefly.

The Mechanical (Traumatic) Factor

The observation of Aschoff (1921)²⁰ that the lesser curvature of the stomach, or "Magenstresse," has a different anatomic arrangement than the rest of the stomach has led many workers in this field to theorize that in the lesser curvature region, the pyloric antrum and the first portion of the duodenum the regions where benign ulcers most commonly occur, since the mucosa is more fixed and smoother than elsewhere and its blood supply is less rich it has less mechanical protective value and consequently is more subject to the traumatic effect of ingested materials. Halperin (1926)²² was one of the first in this country to subscribe to this theory. However the healing time of acute ulcers produced by the submucosal injection of silver nitrate was not affected by massaging the region with bread crumbs until congestion occurred according to Ivy (1920).²³ Callagher (1927)^{10a} found the gastric mucosa of dogs quite resistant to trauma produced by the application of clamp. Bagio (1927)²⁴ was able to produce lesions of the gastric mucosa by infolding the anterior gastric wall with sutures producing partial obstruction; erosions and ulcers occurred in the infolded portion of the mucosa, and directly opposite in the areas where ingested material impinged on the mucosa.

This theory was emphasized in conjunction with the acid peptic factor by the Mayo clinic group as a result of their observations on Mann-Williamson dogs. Mann^{25, 26, 27, 28} called attention to the fact that ulcers in these dogs could not be due to the operative trauma because they developed after the suture line had healed. He observed particularly that the ulcers occurred at the same site just distal to the suture line in the jejunum and often opposite the stomach and attributed this to the jet effect of material squirted through the pylorus by peristaltic waves. Moreover the lesions developed more rapidly if the stomach were small than with a large stomach. Morton (1927)^{27a} noted that when Mann-Williamson dogs that had already developed jejunal ulcers were reoperated upon performing an anterior gastroenterotomy the original jejunal ulcers healed but other jejunal ulcers developed where the new jet of chyme impinged on the jejunal mucosa. The importance of the lesser curvature as an area susceptible to trauma was also emphasized by Morton (1927-1928).^{29, 30, 31, 32}

Mucosal defects produced by snipping out areas of mucosa took longer to heal on the lesser curvature and in the antral region than in other areas, and when such defects were produced in conjunction with the Mann-Williamson procedure only those defects on the lesser curvature became chronic ulcers. Like wise when patches of jejunum were implanted in the stomach of dogs then subjected to the Mann-Williamson procedure only those patches in the lesser curvature region exhibited ulcers. Concerning two of the ulcers in McCann's (1929)²³⁹ dogs which had a modified Schulinsky procedure performed, numerous dog hairs were found embedded in the base of one, and the other, which was perforated had a piece of turnip protruding through it. The force required to embed these objects was attributed to the 'jet effect'.

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human breast fat³⁶ resulted in the development of gastric or duodenal ulcers in a rather low percentage of animals. Since it was demonstrated³⁷ that fractures in man, or fractures or curettement of the bone marrow in dogs failed to cause any stimulus of gastric secretion it was concluded that the ulcers obtained were on the basis of fat emboli which they thought produced localized areas of anemia more susceptible to the digestive activity of the gastric juice.

Considerable interest has been shown by clinicians for many years in the relationship of caffeine containing drugs to ulcer development. Caffeine and caffeine containing beverages have been shown to stimulate gastric secretion in man and the cat but not in the dog.^{38, 39, 40} Gastric ulcers or erosions have been produced in cats⁴¹ and guinea pigs⁴² by the administration of caffeine in beeswax. The mechanism by which these ulcers are produced has been studied rather thoroughly on a histologic basis by Roth and Ivy (1945)⁴³. They found that with the prolonged administration of caffeine a vasodilatation and vascular engorgement and stasis developed in the gastric wall these were thought to result in local anoxia and increased capillary permeability, resulting in an ideal site for the initiation of digestion by the highly acid gastric juice. Baron ofsky (1945)⁴⁴ has shown that the vascular stasis produced by splenic vein obstruction abets the ulcer diathesis.

The Allergic Factor—Shapiro and Ivy (1926)⁴⁵ produced acute gastric ulcers in previously sensitized or passively immunized dogs or rabbits by injection in the submucosa of various antigens such as beef protein albumin, etc. They felt that a similar phenomenon might occur in man as a result of sensitization to some type of protein to which he is repeatedly exposed the process then being enhanced by the trauma of ingested food and acid peptic digestion. Recently, Warransteen's (1948)⁴⁶ group have sensitized dogs in a somewhat similar manner and observing the gastric and duodenal mucosa in the sensitized animals during the intravenous injection of the antigen concerned found that a marked edema developed. With repeated administration of antigen three of six sensitized dogs developed ulcers and when histamine in beeswax was given daily to another group of sensitized dogs the rapidity of ulcer development was markedly increased over that normally expected.

The Nutritional Factor—The nutritional status of the body as a whole appears to be an important factor in determining mucosal resistance to acid peptic digestion. According to Bollman and Mann (1927)⁴⁷ in animals with an ilek fistula resulting in disturbances of protein metabolism there is a high incidence of chronic duodenal ulcer. Although guinea pigs rarely develop spontaneous peptic ulcers Smith and McConkey (1933)⁴⁸ found that 26 per cent of their guinea pigs maintained on a diet deficient in vitamin C developed chronic ulcers similar in location and appearance to those seen in man.

It was felt by Weiss and Aron (1933)⁴⁹ that the ulcers resulting from Mann and Williamson's procedure might be due to digestive disturbances especially with regard to protein metabolism cachexia anemia and atrophy of the gastric mucosa when histidine and tryptophane or histidine alone were given daily to their Mann-Williamson dogs they failed to develop ulceration as late

as ten weeks after operation. Moreover, Fauley and Ivy (1936)¹⁴⁸ found that a special easily assimilable diet would delay the appearance of ulcer in Mann-Williamson dogs, but if such dogs survived more than sixteen weeks nearly all the dogs developed ulcer. Nutritional changes in Mann-Williamson dogs, and especially a fall in serum proteins, were noted by Flood and Mullins (1936),¹⁵ but six of eleven of their dogs which were given histidine daily developed jejunal ulcer. Likewise, Wu (1937)³⁹ was able to demonstrate jejunal ulcers in four of six Mann-Williamson dogs to which histidine was administered daily, and Sandweiss' group (1937)⁴³⁷ demonstrated ulcers in all their histidine-treated dogs which survived the Mann-Williamson procedure more than three days.

✓The studies of Weech and Page (1937)⁵¹⁶ give further indication of the importance of protein metabolism in relation to ulcer development. Of twenty-two dogs fed on a diet deficient in protein for an average period of ninety days, eight developed ulcers of the stomach or duodenum and another five showed gastric or duodenal erosions. Li and Freeman (1946)³²³ demonstrated an even higher incidence of gastroduodenal ulceration in dogs on a protein deficient diet; twelve weeks appeared to be the minimum time of such a diet necessary to produce ulceration. The development of perforated duodenal or jejunal ulcers after pylorectomy in hypoproteinemic dogs has been shown by Meeray, Larden and Ravdin (1937)³⁴⁸. Thus it appears that the state of nutrition, particularly with regard to protein metabolism, is of great importance in ulcer development; however, the findings of Weiss and Aron that histidine is the single important essential amino acid concerned have not been substantiated. These considerations have resulted in the recent popularity of various regimes, such as that of Kuguro's group⁴³⁴ for the treatment of peptic ulcer by the administration of protein hydrolysates.

✓The Inflammatory Factor—The inflammatory basis of ulcer development was strongly urged by Konjetzny (1931)³² on the basis of pathological studies. Since gastric juice will not ordinarily digest normal gastric or duodenal mucosa, he felt that peptic ulcers developed in a damaged mucosa as a result of gastritis or duodenitis, and never developed in a normal gastroduodenal mucosa.

Several attempts have been made to show that peptic ulcer is an infectious disease, the result of invasion of a specific organism. Turek (1906)⁴⁴³ produced ulcers of the stomach and duodenum by feeding dogs certain strains of *Lacillus coli*, but was unable to prevent the healing of artificially produced gastric mucosal defects by the intravenous injection of colon bacilli obtained from feces of patients with peptic ulcer. The theory of elective localization of streptococci was propounded by Rosenow (1913-1916)⁴²⁻⁴³. Certain strains of streptococcus (viridans and hemolyticus) were isolated from the ulcers of clinical patients at the time of operation, and intravenous injections of these organisms produced gastric or duodenal ulcers in various experimental animals. These results were confirmed by Hardt (1916)²⁷⁴. Moreover, organisms obtained from such experimentally produced ulcers when injected intravenously in another experimental animal would again cause ulcer formation. The clinical im-

portance of foci of infection, harboring these organisms, in the tonsils, teeth, gall bladder, and appendix was stressed by Rosenow. Hoffmann (1925) isolated a gram negative rod from the gastric contents of ulcer patients and felt that it represented a specific organism, since intra abdominal or intra muscular injection in guinea pigs was followed by the development of gastritis, duodenitis or ulcer, and these lesions could be reproduced after passage through several animals. As a result of immunologic studies with organisms isolated from ulcers in clinical patients and the serum from those patients, Saunders (1930)⁴³⁰ thought that a nonhemolytic streptococcus of the alpha type was the specific organism involved.

✓ The multiplicity of organisms to which ulcer causation has been attributed seems to cast a shadow of a doubt on any specific bacterial theory and to suggest that such organisms may have been secondary invaders. In addition there is some evidence in opposition to such theories. Hardt (1916)²⁰⁴ was unable to produce ulcers in rabbits by the intravenous injection of *B. coli*. Wilenski and Geist (1916)⁵²⁴ were unable to influence the healing time of artificially produced mucosal defects in the stomach of cats despite repeated injections of various strains of streptococci cultivated from human ulcers. Ivy (1920),²⁴⁰ producing ulcers by silver nitrate injection in the gastric mucosa was unable to alter the healing time of these ulcers by massaging them with various strains of streptococci (viridans, hemolyticus) and staphylococci. He was also unable to produce ulcers by injections of streptococci in the gastropiploic vessels or by feeding streptococci to healthy dogs. It is interesting that two dogs with distemper, who had achlorhydria developed duodenal ulcers. Ivy thought that the relatively high acidity occurring in the normal stomach was incompatible with the life of most bacteria and that the production of ulcers by "specific bacteria" was attributable to nutritional disturbances or foreign protein reactions.

The Neurogenic Factor

✓ The frequent appearance of peptic ulcer in emotionally overactive, driving or aggressive individuals or in those whose occupation of necessity subjects them to a life of high tension such as for example physicians and taxicab drivers has led many clinicians to suppose that a neurogenic factor is involved in ulcer genesis. This has resulted in various types of clinical application. Crile (1931, 1933)^{100, 101} felt that in such "hyperkinetic" individuals there was a tremendous overactivity of the sympathetic nervous system resulting in pylorospasm (and retained gastric secretion). On the basis of this theory he advocated (and practiced) suprarenal denervation for uncomplicated peptic ulcer but this mode of therapy never gained any great popularity. The reintroduction by Dingstedt (1942)¹¹⁰ of vagus resection as a surgical procedure useful in treating peptic ulcer is based on his observation that the ulcer patient has an excessive continuous secretion of acid gastric juice which is particularly deleterious at night when unneutralized by food. This secretion is said to be mediated through the vagus nerves by psychic stimuli. The work of Wolf and Wolff (1943)⁵²⁶ showing the relationship of emotional activity to gastric secretion has stimulated the interest of psychiatrists and psychosom-

ists in the disease. Recent studies by Boerema (1948)⁶ of the increased incidence of ulcer in Holland during the World War II concluded that ulcers occurred on the basis of neurogenic spasms of the gastric and duodenal musculature resulting in localized areas of ischemia.

The spontaneous occurrence of acute perforating gastric or duodenal ulcers in three patients who had been operated on for cerebellar tumors led Cushing¹⁰² to suggest a definite relationship between ulcer causation and the midbrain. Keller, Hare, and D'Amour⁶ were able to produce hemorrhagic erosions in animals with experimental lesions of the brain stem.

The effects of vagus resection and the relationship of the vagus nerves to gastric secretion are discussed in more detail elsewhere. It is interesting to note however, that experimentally gastric ulcers have been produced in rabbits as a result of bilateral vagotomy.^{10 40 50} However vagotomy in dogs has failed to produce ulcerative lesions and chronic stimulation of one vagus nerve in the dog has not resulted in ulcer formation.⁶¹ Baver and Mann (1931)⁴² minimized the importance of nerve impulses in ulcer development by showing that neither bilateral vagotomy nor resection of the splanchnic nerves would prevent the development of jejunal ulcer in a Mann-Williamson dog. However the administration of a cholinergic drug pilocarpine by various parenteral routes has resulted in the development of acute ulcers in rabbits.^{163 164 3} These lesions were attributed by Underhill and Freiheit (1928)⁶⁴ to localized areas of ischemia as a result of the excessive increase in gastric motility. Experimental ulcers have also been produced by interference with the sympathetic nervous system in various ways: by bilateral adrenalectomy,^{3 9 21} section of the splanchnics,^{10 120} and removal of the prevertebral (celiac superior and inferior mesenteric) ganglia.¹¹⁴ It should be stated that many of these experimentally produced ulcers were not at all like those seen in man.

Years ago Alvarez (1932)⁸ after reviewing the experimental work up to that time listed five ways in which he thought nervous influences might act to produce peptic ulcer and it seems that these are still applicable. These mechanisms were:

- 1 An increase in acidity and peptic activity of the gastric juice (actually a result of an excessive volume of secretion)
- 2 A diminution in the amount of mucus secreted
- 3 An ischemia of the tissues produced by spasm of the blood vessels or of the muscle of the stomach
- 4 The possibility of pancreatic and biliary secretions drying up as does the saliva under emotional stress
- 5 Stagnation of gastric contents with increased acidity is the result of pylorospasm

Miscellaneous

L Peptic ulcers are known to occur as an occasional complication of severe burns. Harkins (1938)³ reviewed the literature on the subject of these "burning" ulcers and thought that a septic cause was the most likely since they most frequently occur in association with large sloughing infected burns. Others have attributed the occurrence of these ulcers to protein deficiency.

Gastric and duodenal ulcers have been produced experimentally by numerous other methods, none of which seem closely related to the process of development of ulcer in man. These methods include exposure of the gastric mucosa to roentgen rays,⁸⁷⁸ administration of toxins such as cineophen^{461, 472} and administration of posterior pituitary extract.^{116, 218}

Thus in summation it may be said that on the basis of the evidence at hand the acid peptic factor appears to be the most important in the etiology of peptic ulcer but the mechanical factor and the neurogenic factor may play an important role and the resistance of the tissues to digestion as determined by a variety of factors, is of great consequence. It must not be forgotten that the acid peptic factor cannot be entirely separated from the neurogenic factor and that all the aforementioned factors are interrelated.

OPERATIONS FOR PEPTIC ULCER

Indications for Operation

✓ It is not within the scope of this work to enter into any extended discussion with regard to indications for operation for ulcer. In general there is a fairly close agreement, among both internists and surgeons concerning these indications. All are in agreement that a diagnosis of perforation merits an immediate emergency operation usually a simple closure of the perforation either by suture or by an omental graft^{23, 24} is the procedure of choice although resection has been occasionally recommended.

There is rather general agreement that operation is necessary for gastric ulcers which do not heal promptly⁴ because of the possibility of the presence of early carcinoma, for ulcers which cause cicatricial obstruction to the gastric outlet for ulcers including postoperative gastrojejunal ulcers which do not respond to an adequate trial of medical therapy, and for ulcers which have been the cause of repeated episodes of hemorrhage.^{5, 6, 21, 24} Only in the matter of surgery in relation to an actively bleeding ulcer is there a wide diversity of opinion, which ranges from the idea of medical treatment for all with immediate feeding as advocated by Muelengracht (1939)²⁵ and Andresen (1939),¹¹ to the extreme of advising early operation for all severely bleeding ulcers, as does Finsterer (1939).¹⁴ The length of time the patient has been bleeding, the severity of the hemorrhage and the age of the patient as emphasized by Blackford (1939)⁴⁴ are important considerations here and the majority of surgeons such as Hinton (1938)¹⁹ and Wangensteen (1940)³² choose a middle ground between these two extremes.

Variety of Operations for Ulcer

When surgery has been decided upon for the ulcer patient the surgeon has at his disposal a great variety of procedures from which to choose the one which will benefit his patient to the greatest degree. Many of these have proved to be hopelessly inadequate and do not merit discussion others by their iniquities have proved educational particularly with regard to the pathophysiology of the upper gastrointestinal tract. None of the operations in use today gives 100 per cent perfect results but surgeons and experimentalists are

constantly striving toward such a goal, and for that reason a number of procedures will be discussed briefly, the emphasis being placed on gastric resection and its variants.

Vagus Resection—Bilateral resection of the vagus nerves as advocated by Latarjet, and as recently reintroduced and popularized by Dragstedt (1943 1946),^{12 123 124 4 5} Moore (1946 1947)^{26 2 5} (Timson (1946 1947)^{102 4 5} and their colleagues is a procedure which must still be considered in the experimental stage. When one considers the experience the surgical profession has had with gastroenterostomy, one can agree with Small (1947)^{4 5} who in his thorough review of the subject stated that a good many years will have to pass before such an operation is adequately evaluated. Meanwhile in the period of evaluation it seems reasonable to state that if this procedure is complicated by a variety of other procedures done in conjunction with it no long term evaluation of the pure operation will be possible. Moreover since the presence or absence of carcinoma in a gastric ulcer can be determined with certainty only under the microscope⁴ it seems fair to state that vagus resection should never be used alone as definitive treatment for gastric ulcer. Also since vagus resection results in considerable gastric atony and marked prolongation of the gastric emptying time^{9 2 3 42 4 5} it should not be used alone as definitive therapy for ulcers already causing obstruction. One cannot help wondering like Warren (1947)¹³ if the obstructive effect of vagotomy may not interfere with the neutralization of gastric acid by the duodenal juices and if the neutralization process may not be further diminished by a decreased secretion of gastric mucus.

The most striking early result of vagus resection is an immediate cessation of ulcer pain in almost all cases,^{124 264 4 5} as well as a healing of the ulcer as manifested by x-ray examination in a relatively short period of time in the majority of cases. The volume of gastric secretion is diminished particularly with regard to that secretion occasioned by central stimuli,^{4 5} and the volume and acidity of juice secreted in response to alcohol is diminished,²⁹ but the secretory response to histamine remains the same. Theoretically the operation must consist of a complete section of all vagus fibers since it has been shown¹²⁴ that unilateral vagus section has no effect on gastric secretion although Walters (1947)^{4 5} and Laufen (1948)^{42 4} pointed out that excellent clinical results have been obtained in patients who have had incomplete vagal section as indicated by the insulin test. The most troublesome ensuing complication is a decreased gastric motility with stagnation of gastric contents annoying sensations of fullness and frequent regurgitation of ingested material which may be so severe as to require pyloroplasty gastroenterostomy or gastric resection. Diarrhea and cardiospasm may also occur.

The early enthusiasm for this operation of Dragstedt (1945)^{12 1 4} who reported cures in 33 to 39 patients and who later reported (1947)¹²¹ 160 vagotomies (some associated with gastroenterostomy) during a four year period with only 5 (3 per cent) showing even suggestive evidence of recurrence must be tempered with the knowledge that an increasing number of poor results are being reported from this operation. While the mortality rate is generally considered

to be almost 0,³⁰¹ and Drigstedt¹²¹ reported no deaths in 150 cases the Mayo Clinic group (1947)⁴⁰⁰ reported 4 deaths 1 from a perforation of a duodenal ulcer, in a series of 84 vagus resections a mortality rate of almost 6 per cent which is higher than the mortality rate for gastric resection in the most experienced hands. Weeks, Ryan, and Van Hoy (1946)⁵²⁷ reported 2 deaths 1 due to perforated duodenal ulcer the other due to cardiac arrest on the operating table when traction was exerted on the vagus nerve. Moore (1947)³⁴¹ considered that only 87 per cent of the results in a series of 74 vagus resections could be regarded as good. 5 patients (6.7 per cent) had either symptoms of recurrent ulcer or actual demonstration of such a recurrence. 2 others had bleeding, presumably of ulcer origin, about two weeks postoperatively, and 1 others had annoying symptoms sufficiently severe to detract from the results. Of 54 cases reported by Walters group (1947)⁴ the ulcer failed to heal in 7 (8.3 per cent). Warren (1947)¹¹ reported that in a series of 13 vagotomies 1 patient developed a new ulcer and 2 others had retention severe enough to require further surgery.

Furthermost caution with regard to vagus resection should also be considered by a survey of certain experimental work. As recorded previously although Hartzall (1929)⁷⁹ reported a reduction in gastric acidity after bilateral vagus section in dogs, Vanzant (1931)⁴ working with the same dogs 2½ years later found their secretion approximately normal. Shapiro and Ber, (1934)⁴⁴ presented evidence that after vagus section the stomach achieved some degree of autonomous control of acid secretion this control perhaps being localized in the plexuses of Meissner and Auerbach. It has been shown by Beaver and Mann (1931)⁴ Oliver (1947)³⁸⁸ and Seltzer's group (1947)⁴³⁴ that vagotomy fails to prevent the appearance of jejunal ulcers after the Mann-Williamson procedure in dogs. Only Hartman and Hooley (1948)⁶ reported that such ulcers were prevented by vagotomy. They as well as Lallouch (1947),³⁰⁰ found that vagotomy in dogs did not prevent the production of ulcers by histamine in lacc wax although Lallouch noted that the appearance of the ulcers was slightly delayed.

Without being unduly pessimistic therefore it should be stated that the operation of vagus resection merits considerable further evaluation and should be employed with considerable caution in selected cases and not as a routine procedure.

Pyloroplasty—For many years pyloroplasty of various types including gastroduodenostomy with excision of the ulcer was advocated particularly by the Mayo Clinic group (1930)²³⁰ and Finney (1929)¹¹³. Such procedures have some experimental basis in the work of Flann's group (1931-1933)¹³⁸⁻¹⁴ Morton (1934),⁵ and others previously reported. However they are applicable only in certain situations and more specifically are of no value in dealing with those ulcers frequently found on the posterior wall of the duodenum eroding into the pancreas. In addition the results of such procedures have proved grossly unsatisfactory in the hands of many.²³²⁻²⁹ Hence no attempt will be made to compare such procedure with more thorough and perhaps more statistically justifiable operations.

✓ **Gastroenterostomy**—Gastroenterostomy was introduced by Wolsley in 1881 and during the next forty to fifty years a great deal of hope was maintained for this operation as a curative procedure for peptic ulcer. During the second and third decades of the twentieth century, this procedure was gradually abandoned in favor of a more radical resection by European surgeons, but American surgeons were much more tenacious in their opinion that posterior gastrojejunostomy was a satisfactory operation. As cases were followed longer and longer the *bête noire* of jejunal or marginal ulcer appeared more and more frequently, substituting a more undesirable condition for the original ulcer. Some of the earlier figures for the incidence of jejunal ulcer after gastroenterostomy may reflect an inadequate follow up period and poor methods of analysis of results or might be colored by the aversion of a group of surgeons to the more radical operation. In 1910 W. J. Mayo³³⁶ reported only 3 jejunal ulcers in 1141 gastroenterostomies. Judd² in 1921 reported an incidence of 1.2 per cent jejunal ulcer in 4324 gastroenterostomies done at the Mayo Clinic. Balfour³⁴ reported an incidence of 1.6 per cent jejunal ulcer for the same institution in 1926, but this figure was obtained by the fallacious method of comparing the number of gastroenterostomies done during the period concerned with the number of gastrojejunal ulcers operated on. This group felt that gastroenterostomy yielded approximately 90 per cent good results. Likewise Movshin³³⁹ in 1928 reported an incidence of only .4 per cent jejunal ulcer with his gastroenterostomies. An incidence of 1.7 per cent jejunal ulcer after gastroenterostomy was reported in 1925 by Walton³⁴⁰ but nine years later his figure had risen³⁴¹ to 3.4 per cent.

As the years advanced it became more apparent that such figures were a false picture of the true value of this operation. DeTrikats (1926)^{342, 343} reporting on the experience of the University of Budapest as early as 1926 gave an incidence of 1.8 per cent jejunal ulcers after gastroenterostomy and felt that only 50 per cent of the patients so treated could be classified as excellent results. When a von Eiselsberg pyloric occlusion was combined with a gastrojejunostomy, this figure reached 21 per cent. Haberer (1921)³⁴⁴ reported fourteen jejunal ulcers in seventy-one patients who had the von Eiselsberg procedure. Lewinohn (1925)³⁴⁵ in this country startled more complacent surgeons by recording an incidence of 3.4 per cent gastrojejunal ulcer after gastroenterostomy, both with and without pyloric exclusion. Other more recent figures illustrating the increasing occurrence of jejunal ulcer after gastroenterostomy as the follow up period increased are: 2.4 per cent reported by Strauss group (1924)³⁴⁶; 4.8 per cent (including those suspected clinically) reported by Newburger (1937)³⁴⁷; who noted that every case in which a patient under 30 years of age had a gastroenterostomy proved to be a failure; 12.3 per cent reported by Graham (1938)³⁴⁸; 16.4 per cent reported by Hinton (1935)³⁴⁹ and five years later dealing with material from the same clinic 24.4 per cent reported by Church and Hinton (1940)³⁵⁰. Wright (1935)³⁵¹ reported the results of a collective inquiry by the Fellows of the British Association of Surgeons indicating that in 2907 gastroenterostomies there had been 220 proved and suspected jejunal ulcers, an incidence of 7.5 per cent. The experience of Hurst and Stewart (1928)³⁵² is per

to be almost 0³⁶⁰ and Dr. Dugstedt¹²¹⁸ reported no deaths in 150 cases, the Mayo Clinic group (1947)⁴²⁹ reported 4 deaths 1 from a perforation of a duodenal ulcer in a series of 84 vagus resections a mortality rate of almost 6 per cent which is higher than the mortality rate for gastric resection in the most experienced hands. Weeks, Ryan, and Van Hov (1946)¹ reported 2 deaths 1 due to perforated duodenal ulcer the other due to cardiac arrest on the operating table when traction was exerted on the vagus nerve. Moore (1947)³⁶ considered that only 87 per cent of the results in a series of 74 vagus resections could be regarded as good, 5 patients (6.7 per cent) had either symptoms of recurrent ulcer or actual demonstration of such a recurrence 2 others had bleeding presumably of ulcer origin, about two weeks postoperatively and 1 others had annoying symptoms sufficiently severe to detract from the results. Of 84 cases reported by Walters group (1947)⁴¹⁹ the ulcer failed to heal in 7 (8.3 per cent). Warren (1947)³¹³ reported that in a series of 15 vagotomies, 1 patient developed a new ulcer and 2 others had retention severe enough to require further surgery.

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Gastric Resection—

Gastroenterostomy versus gastric resection While the evidence against gastroenterostomy delineated here was being accumulated a long controversy raged in the surgical literature between the proponents of gastroenterostomy and those who favored gastric resection. European clinics, such as that of Haberer (1920),²⁰⁰ and the University of Budapest (1926)^{117 111} on the basis of their own comparative studies found that the incidence of marginal ulcer after gastroenterostomy was excessively high and the results rather poor, and at a relatively early date they began to resect more stomach for ulcer. A. A. Berg (1928, 1930)^{44 49} was one of the early advocates of gastric resection in this country, and for many years was almost alone in this regard, the resistance to this radical approach to the ulcer problem being remarkably great throughout the country. Walters (1932)⁴⁹ as a result of comparisons he made between resected specimens seen in German clinics and similar specimens at the Mayo Clinic felt that there was a geometrical difference between the ulcers seen in Europe, which were associated with a marked gastritis and those in America which were not. He thought gastric resection justifiable in Europe but not in this country. Jejunal ulcers after gastroenterostomy were explained as the results of a conservative procedure in patients in whom there was an associated gastritis. If this were true the incidence of gastritis in America must be high indeed if Newburger's figures¹²³ are correct.

However as the years passed by more evidence accumulated that gastroenterostomy was a partial failure as a curative procedure for ulcer and more surgeons were converted to the use of gastric resection. At present, the great majority of surgeons^{1 104 234 2 0 241 308 36} though perhaps differing as to the extent of resection advocate gastric resection as the procedure of choice in most cases. A surprising exception is found in Heuer (1944)²⁷ and his associates. These writers although admitting that probably only one third as many jejunal ulcers occur after gastric resection as after gastroenterostomy nevertheless felt this advantage of gastric resection was offset by the higher mortality of this operation in average hands which they expressed as varying in the literature between 2 and 22 per cent with a probable average of 7 per cent. However Lewishohn (1945)²⁰¹ pointed out that in most experienced hands the mortality for gastric resection is only about 2 per cent. Indeed on perusing the recent literature some even lower mortality figures may be found perhaps the result of the increasing number of valuable adjuvants to gastric surgery. For example, a mortality of 1.1 per cent is reported in 368 partial gastrectomies at the Mayo Clinic (1944).⁸ Bartels and Duhin (1947)²⁸ reported 1.6 per cent mortality in 121 successive partial gastrectomies and King (1946)^{2 3} reported no deaths in a series of 75 subtotal gastrectomies. Zollinger⁴¹ in 1940 made an extensive review of the literature in an effort to compare the results of gastroenterostomy and gastric resection and recorded that the reported incidence of jejunal ulcer after gastroenterostomy varied between 2 and 24 per cent while that after gastric resection varied between 0.4 and 10 per cent which is rather convincing evidence that gastroenterostomy is not necessarily the more desirable procedure.

ticularly interesting. They found in routine autopsies on 131 cases with gastrojejunostomy done at some previous time, that 25 (19%) of these cases had gastrojejunal ulcers, and of the 42 cases autopsied more than 9 months and up to nineteen years after operation, 22, or 52 per cent, had gastrojejunal ulcers. Laker (1940),⁸² who made a thorough study of this field, felt that the average incidence of gastrojejunal ulcer after gastroenterostomy is about 15 per cent. It should be said that in nearly all of these series, other cases were recorded as unimproved. Church and Hinton (1940)⁸³ felt that only 24.5 per cent of their gastric and duodenal ulcers subjected to gastroenterostomy could be considered as cured. Experimentally, Watts (1903)⁸¹⁵ has observed the spontaneous occurrence of jejunal ulcer in the dog after gastroenterostomy and Dott and Lim (1923)⁸¹⁵ have recorded a high incidence of such ulcers after gastroenterostomy combined with pyloric occlusion.

A gastroenterostomy which is properly placed near the pylorus is commonly thought of as emptying, by gravity drainage, yet the experimental work of Cannon and Blake (1905)⁸⁴ many years ago showed that the intra abdominal pressure relationships made this impossible. If the pylorus remained patent food went through the duodenum rather than the stoma and Cannon and Blake observed that if the stomach was stretched by ingested material, obstruction might occur in the efferent loop by its compression against the gastric wall thus resulting in the 'vicious circle' which used to be seen so often clinically. Case (1925)⁸⁵ studied fluoroscopically patients who had had gastroenterostomies and found that in successful operations the emptying time was shortened to an average of three hours and forty minutes.

Burget and Steinberg (1922)⁸¹ and Elman (1929)⁸¹² observed that in dogs with posterior gastroenterostomies, duodenal regurgitation took place through the stoma the stomach containing bile almost constantly and acid test meals were rapidly neutralized (in sixty to ninety minutes). Herein was supposed to reside the beneficial effect of gastroenterostomy and since high acidity seems to be the most important factor concerned in the development of jejunal ulcer as will be developed later in this paper the postoperative acidity should be of some importance. Holman and Sindusky (1938)²³⁰ reviewed the literature on this subject and found that a large number of writers claimed a reduction in acidity of 30 to 60 per cent, although some said there was no change. It was noted that most of these analyses had been done with various test meals and in a somewhat unstandardized manner. Holman and Sindusky, in their own series of seventy four cases in which the gastric analyses were done by a standardized method using histamine found that the reduction in gastric acidity fairly uniformly attained with gastric resection is not possible with gastroenterostomy.

Because of the high incidence of postoperative jejunal ulcers gastroenterostomy is very seldom employed by most surgeons in ulcer therapy today. It has not been abandoned however but is reserved chiefly for poor risk cases and especially those with obstructed atonic stomachs and low gastric acidity⁸⁴⁶ since it is in this group that gastroenterostomy has given the best long term results.

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3. *Altered physiology after gastric resection*

(1) *Acidity* The beneficial effect of gastric resection for ulcer may be said to reside in (1) a diminution of the gastric acidity, (2) a removal of part or all of the 'ulcer bearing' portion of the stomach and duodenum, and (3) a decrease in the emptying time of the remaining stomach. Winkelstein and Berg (1938)²²³ listed five factors which unite to determine the postoperative acidity after gastric resection. These factors were (1) removal of the antrum, abolishing the chemical phase (if Edkins hypothesis is correct), (2) the extent of resection determining the amount of fundic secretory tissue removed, (3) the amount of regurgitation of duodenal fluids which occurred through the stoma, (4) the degree of vagus nerve irritability and (5) the amount of gastritis present. These writers found that it was possible to produce achlorhydria by extensive resection in only 50 per cent of patients with duodenal ulcer with a high preoperative acidity, but stated that in twenty six such patients in whom extensive resection was combined with unilateral vagotomy achlorhydria was consistently produced.

What can be expected of gastric resection as concerns a reduction in acidity? Lewison and Linzbach (1927)²⁰ reported that in a series of 85 subtotal gastrectomies 64 patients had postoperative achlorhydria. Klein (1927)²²⁴ reported that "partial" gastrectomy produced immediate hyp acidity or an acidity in 78 per cent of patients with gastric ulcer but in only 18 per cent of patients with duodenal ulcer, however after six months these percentages rose to 100 and 66 per cent respectively. Klein was unable to explain these later changes but thought they might be due to a lowered vagus tone or to a diminished irritability of the remaining parietal cells. Lake (1928)²²⁵ found that achlorhydria was produced in 50 of 51 of his cases as a result of partial (half) gastrectomy. 97.5 per cent of these cases were classified as excellent results and he stated that no jejunal ulcers developed in this series. All the patients studied by Shay and Harrison Cohen (1936)⁴² had achlorhydria after partial gastrectomy. The importance of the regurgitation of the intestinal contents at the stoma was emphasized by St. John's group (1939)⁴³ who found that in 26 resections bile was present in the stomach in all except 2 that the peptic activity of the gastric contents was markedly reduced in all and that free hydrochloric acid was absent in 22 cases diminished in 3 and normal in 1. Iliet and Marshall (1937)²²⁶ recorded that 64 per cent of their gastrectomized patients had postoperative achlorhydria or a free acid of less than 10 per cent.

It should be emphasized that most of these earlier studies were done using various test meals which are incapable of eliciting the maximum acid secretory response possible with histamine. Using histamine Milnes (1936)²²¹ noted that 53 to 60 per cent of ulcer patients with subtotal gastrectomy developed achlorhydria. In 31 gastrectomized patients Strauss and his colleagues (1937)⁴⁴ found achlorhydria to histamine in only 15 patients but a marked reduction in acidity in 25; these workers felt that the clinical results were not correlated with the postoperative acidity but it is noteworthy that the only patient with gastroduodenal ulcer in their series had a high postoperative acidity. Tomoda

and Aramaki (1935)²⁰⁰ reported that after Billroth II resections the acidity was 'in most cases' reduced or absent. The histamine analyses reported by Heuer and Holman (1943)²⁰¹ indicated that in 63 resections for duodenal ulcer 17 patients were achlorhydric, 15 had a low acidity and 31 had a high postoperative acidity, while in 25 resections for gastric ulcer, 18 had postoperative achlorhydria, 7 had a low postoperative acidity and in 2 there was no change in the acidity. There was a considerable variation in the extent of these resections, explaining the marked differences in postoperative secretion. Heuer and Holman were unable to find any correlation between these acid values and the clinical results and since 3 of 11 patients with two thirds or more of the stomach resected showed an acid response to histamine but had good results they felt that the chances of ensuring achlorhydria or better results by increasing the size of the resection beyond a moderate one were rather small. Lewisohn (1945)²⁰² recently stated that with a three fourths to four fifths resection of the stomach anaclidity was observed in 60 per cent of the patients after operation.

Patients who had had a variety of operative procedures for ulcer were studied by Wapenstein and Lamm (1942)²⁰³ eliciting the maximum secretory response with three successive doses of 0.5 m. of histamine. After only two procedures namely a three fourths gastric resection with a Hofmeister retrocolic anastomosis and a Finsterer three fourths resection for exclusion with removal of the antral mucosa was any significant percentage of achlorhydria found. With the first operation 52 of 82 patients showed achlorhydria and of 11 patients who had the second type of procedure showed it both figures out to be approximately 63 per cent. It is again noteworthy that in neither these two groups of patients did any jejunal ulcers occur.

On the experimental side the importance of the factor of neutralization was emphasized by the work of Portis and Portis (1926)²⁰⁴. After subtotal gastrectomy in dogs they found no free acid in the remnant of the main stomach but a small Pavlov pouch continued to secrete free acid. Stemberg, Brough and Vidgoff (1927)²⁰⁵ emphasized the same factor by resecting the antrum with gastrojejunostomy in dogs they found the free acid was reduced or absent but when the duodenal contents were then deviated to the terminal ileum the acidity in the fundus promptly rose to high levels. If results in dogs are applicable to man the work of Fauley, Strauss, and Ivy (1932)²⁰⁶ and Shapiro and Berg (1934)²⁰⁷ should temper enthusiasm for subtotal gastrectomy. Both these groups emphasized that the gastric acidity returned to normal levels several months after a subtotal gastrectomy. Shapiro and Berg thought the size of the stoma was especially important as an influence on the amount of regurgitation (and thus dilution and neutralization) that occurred.

(2) Emptying Time. The early findings of Case (1925)²⁰⁸ indicated that the emptying time is markedly decreased after gastric resection. He noted an average emptying time of fifteen minutes to one hour after a Billroth I resection but an emptying time of four and one half hours after a Polya modification of the Billroth II procedure. Both experimental and clinical observations made by Meerav, Barden and Raydin (1937)²⁰⁹ indicated that if human

✓ *Altered physiology after gastric resection*

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✓ What can be expected of gastric resection as concerns a reduction in acidity? Lewisohn and Ginzburg (1927)³⁴ reported that in a series of 85 subtotal gastrectomies 64 patients had postoperative achlorhydria. Klein (1927)³⁵ reported that 'partial gastrectomy produced immediate hyposecrecy or anacidity in 76 per cent of patients with gastric ulcer but in only 18 per cent of patients with duodenal ulcer, however after six months these percentages rose to 100 and 66 per cent respectively. Klein was unable to explain these later changes, but thought they might be due to a lowered vagus tone or to a diminished irritability of the remaining parietal cells. Lale (1928)³⁶ found that achlorhydria was produced in 50 of 51 of his cases as a result of partial (half) gastrectomy, 97.5 per cent of these cases were classified as excellent results, and he stated that no jejunal ulcers developed in this series. All the patients studied by Shaw and Cershon (1936)³⁷ had achlorhydria after partial gastrectomy. The importance of the regurgitation of the intestinal contents at the stoma was emphasized by St. John's group (1939)³⁸ who found that in 26 resections bile was present in the stomach in all except 2 that the peptic activity of the gastric contents was markedly reduced in all and that free hydrochloric acid was absent in 22 cases diminished in 3 and normal in 1. Ishley and Marshall (1937)³⁹ recorded that 64 per cent of their gastrectomized patients had postoperative achlorhydria or a free acid of less than 10 per cent.

✓ It should be emphasized that most of these earlier studies were done using various test meals which are incapable of eliciting the maximum acid secretory response possible with histamine. Using histamine Milnes (1936)⁴⁰ noted that 75 to 60 per cent of ulcer patients with subtotal gastrectomy developed achlorhydria. In 31 gastrectomized patients Strauss and his colleagues (1937)⁴¹ found achlorhydria to histamine in only 18 patients but a marked reduction in acidity in 23; these workers felt that the clinical results were not correlated with the postoperative acidity but it is noteworthy that the only patient with gastrojejunal ulcer in their series had a high postoperative acidity. Tomoda

and Aramaki (1935)⁴⁰⁰ reported that after Billroth II resections the acidity was in most cases reduced or absent. The histamine analyses reported by Heuer and Holman (1943)⁴¹⁰ indicated that in 63 resections for duodenal ulcer 17 patients were achlorhydric, 15 had a low acidity and 31 had a high postoperative acidity, while in 25 resections for gastric ulcer, 18 had postoperative achlorhydria, 3 had a low postoperative acidity and in 2 there was no change in the acidity. There was a considerable variation in the extent of these resections explaining the marked differences in postoperative secretion. Heuer and Holman were unable to find any correlation between these acid values and the clinical results, and, since 3 of 11 patients with two-thirds or more of the stomach resected showed an acid response to histamine but had good results, they felt that the chances of ensuring achlorhydria or better results by increasing the size of the resection beyond a moderate one were rather small. Lewisohn (1945)⁴¹¹ recently stated that with a three fourths to four fifths resection of the stomach an acidity was observed in 60 per cent of the patients after operation.

Patients who had had a variety of operative procedures for ulcer were studied by Wangensteen and Lamm (1942)⁴¹² eliciting the maximum secretory response with three successive doses of 0.5 m₂ of histamine. After only two procedures namely a three fourths gastric resection with a Hofmeister retro colic anastomosis and a Finsterer three fourths resection for exclusion with removal of the antral mucosa was any significant percentage of achlorhydria found. With the first operation 52 of 82 patients showed achlorhydria and 7 of 11 patients who had the second type of procedure showed it both figuring out to be approximately 63 per cent. It is again noteworthy that in neither of these two groups of patients did any jejunal ulcers occur.

On the experimental side, the importance of the factor of neutralization was emphasized by the work of Portis and Portis (1926)⁴⁰⁴. After subtotal gastrectomy in dogs they found no free acid in the remnant of the main stomach but a small Pavlov pouch continued to secrete free acid. Steinberg, Brouner and Vidgoff (1927)⁴⁰⁶ emphasized the same factor, by making the *in situ* antrum with gastrojejunostomy in dogs they found the free acid was reduced or absent but when the duodenal contents were then deviated to the terminal ileum the acidity in the fundus promptly rose to high levels. If results in dogs are applicable to man the work of Fauley, Strauss and Ivy (1932)⁴⁰⁹ and Shapiro and Berg (1934)⁴⁰⁸ should temper enthusiasm for subtotal gastrectomy. Both of these groups emphasized that the gastric acidity returned to normal levels several months after a subtotal gastrectomy. Shapiro and Berg thought the size of the stoma was especially important as an influence on the amount of regurgitation (and thus dilution and neutralization) that occurred.

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tomeum is present it may result in nutritional edema at the stoma, and a marked *prolongation of the emptying time after resection*. While fairly rapid emptying is desirable, and a relatively large stoma important in relation to the neutralization of acid by reurgitation of intestinal contents through the stoma, and also important in preventing a "jet effect" producing trauma to the intestine it has been pointed out by Custer Butt, and Waugh (1946)³⁰³ that if the stoma is too large the so called "dumping syndrome" may ensue. This syndrome the result of excessively rapid emptying and perhaps in part a manifestation of resultant hyperinsulinism is characterized clinically by nausea, weakness, warmth, sweating and palpitation which occur after meals and are relieved by lying down. In a series of 500 gastric resections, these authors found 25 such cases an incidence of 5.6 per cent and on the basis of this information advocated the Hofmeister type of anastomosis in preference to the larger stoma of the Polya anastomosis.

There is some evidence that the gastrojejunostomy stoma after resection of the stomach develops some degree of sphincter like activity. Vitkin (1940)⁴³³ studying resected patients fluoroscopically and resected dogs by means of balloons placed at the anastomosis through a gastric fistula noted that there was a rhythmic evacuation of the gastric remnant occasioned by a periodic opening and closing of the anastomosis due to peristaltic contraction of the efferent loop. Schindler and Dailey (1941)⁴⁴² have observed such sphincter like contractions of the stoma through the gastroscope. Kennedy, Reynolds and Cantor (1947)^{47 208} speak of the "true stoma" as being not the circumference of the residual stomach, but only that narrowed jejunal diameter into which the stomach empties found at the lower end of the anastomosis. They have demonstrated both by x ray view and at operation (for incisional hernia four years after resection), contraction of the circular fibers of jejunal musculature in this area in a sphincter like manner with some out pouching of the proximal jejunal wall of the stomach. They arrived at the conclusion that the size of the true stoma remains the same (that is the caliber of the jejunum) regardless of the type of anastomosis.

(3) *Extent of Resection* With certain exceptions the opinion that gastric resection is the elective procedure of choice in most cases of gastric and duodenal ulcer is fairly uniform but there is less unanimity of opinion with regard to the extent of the resection necessary to prevent recurrence of the disease. Graham (1938)¹⁷⁰ advocated a resection of three fourths of the stomach noting that of the four jejunal ulcers which occurred in his series of gastric resections three were in patients who had limited resections. The Lahey Clinic group (1937)²³¹ likewise believed a resection of three fourths to four fifths of the stomach is necessary and Marshall (1945)²³⁰ quoted illustrative cases of gastrojejunal ulcer after lesser resections. Hunt (1941)²³⁴ however believed that such a radical resection interferes too much with the function of the stomach as a reservoir and felt that in the ordinary case hemigastrectomy will provide reasonable assurance that jejunal ulcer will not occur but in cases with excessively high gastric acid he believed in a more radical procedure. Likewise Sanders (1945)⁴³⁶ resected only about one half of the stomach for ulcer but

admitted an incidence of 8 per cent jejunal ulcers after operations for duodenal ulcer

A detailed analysis of eighty eight resections for gastric and duodenal ulcer by Holman and McSwain (1943)²⁹ indicated that all but one of their eleven patients with two-thirds of the stomach resected had achlorhydria or low acidity, and only 25 per cent of those with antral resection had lowered acid. Since they indicated that jejunal ulcers occurred only in those with a free HCl over 60 per cent after resection their conclusion that the clinical results show no relation to the postoperative acidity is rather surprising. Even more surprising is their conclusion that the clinical results were not related to the extent of resection although they indicate that there were no unsatisfactory results in the group with two thirds or more of the stomach resected. It was stated by Bartels and Dulin (1947)³⁰ that in their experience more patients had achlorhydria after resection of less than two thirds of the stomach than in the group with a more radical resection. This is quite surprising in view of what is known concerning the physiology of the stomach. However, they admitted that recurrent ulcers are more frequent after conservative than after the more radical resections.

Rienhoff (1945)³¹ preferred a rather conservative resection going no higher than the mensura angularis on the lesser curvature. With this procedure 40 per cent of his patients were achlorhydric after operation and most of them symptom free and he thus concluded that the success of gastric resection for ulcer depends chiefly on the permanent reduction in gastric acidity. An incidence of 9 per cent jejunal ulcers is claimed by Rienhoff but Wanzenstein (1945)³² analyzing Rienhoff's own figures noted that if the patients with episodes of gastrointestinal bleeding after operation were added to the number of proved marginal ulcers, this figure would reach approximately 21 per cent and in addition another 16 per cent had sufficient pain to be classified as poor results.

In this connection some experimental work done at the University of Minnesota is of interest. Baronofsky and his colleagues (1945)³ performed resections of the Billroth I type of varying extent in dogs. 75 per cent of the dogs with either one fourth or one half of the stomach resected developed ulcers when injected repeatedly with histamine in beeswax but a three fourths resection protected all of the dogs from histamine induced ulcer. Likewise Lamm (1945)¹⁹ in similar experiments showed that a three fourths resection of the Billroth II variety would protect dogs against histamine induced jejunal ulcers while resection of one half or less of the stomach would not. This experimental evidence has been repeatedly emphasized by Wanzenstein (1941-1945)^{303, 310} who observed on the basis of his clinical experience that only after a resection of three fourths or more of the stomach can one achieve as high an incidence of achlorhydria as 63 per cent. Moreover, he claimed that in his experience jejunal ulcers almost never occur after such an extensive procedure.

Most surgeons realize quite well the difficulty encountered in estimating the percentage of the stomach removed at the operating table. No absolutely

Accurate method has been devised for doing this but Wangenstein's group (1940)¹² believed that they can make a fairly close estimate by dividing the stomach into a series of rectangles and triangles and measuring these. In addition they attached considerable importance to the weight and area of the tissue removed, believing that, unless the stomach is tremendously enlarged, the removal of 200 sq cm (measured on the serosal surface) is adequate, as is the removal of 180 to 220 gm of gastric tissue.

✓(4) Varieties of Gastric Resection The original Billroth I operation consisting of the removal of a portion of the stomach and the pylorus and performing a gastroduodenostomy or one of its modifications would appear to preserve the normal physiologic relationship better than other methods providing relatively normal stimulation of pancreatic and biliary secretory activity.¹³ However, Walters (1937)¹²⁷ has shown that a greater reduction in acidity is obtained with some modification of the Billroth II procedure than can be obtained with the Billroth I procedure. Since the experimental work of Lamm (1945)²⁹ and Baronofsky's group (1945)³ has confirmed the clinical impression that an extensive resection is necessary to prevent ulcer recurrence most surgeons like Lahey (1939)^{4, 10} feel that the Billroth I operation might be unsafe especially in cases of duodenal ulcer with edema and induration of the duodenum since the anastomosis might be made under tension or the operator might reduce the extent of the resection in order to insure an anastomosis without tension. Consequently most surgeons^{4, 11, 28, 509} prefer some modification of the Billroth II technique in which the duodenal stump is closed and the jejunum anastomosed to the stomach remnant. The modifications most frequently used are the Polva operation, with an end to side anastomosis the stomach being the entire width of the lumen of the stomach remnant, or the Hofmeister modification of the Polva operation in which a portion of the gastric remnant is closed and the anastomosis made with the remainder. Evidence that one of the variants of the Billroth II type of anastomosis should be preferable to the Billroth I variety was contributed by Steinberg and Proffitt (1932)⁶ who found that they could prevent ulcer formation in dogs which had the Lxalto short circuiting procedure (vide supra) by performing a subtotal gastrectomy with a Polva or Hofmeister anastomosis. ¹

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✗ In certain cases of duodenal ulcer particularly those involving the common duct in the inflammatory process or surrounded by a diffuse inflammatory reaction, removal of the pylorus and of the ulcer is difficult or impossible without damaging vital structures. In this type of case Finsterer (1931)¹³ advocated "resection for exclusion" performing a variation of the Polva anastomosis but not removing the pylorus and pyloric antrum. Although he felt

that he obtained 90 per cent good results with this procedure various surgeons^{28, 29, 30} have noted a high incidence of jejunal ulcer after this procedure, one of the highest figures being 41 per cent quoted by Ogilvie (1938)²⁸. Allen and Welch (1946)²⁹ Wangensteen (1942)³⁰ and others practice such a procedure in difficult cases but stress the importance of removing the antral mucosa in order to prevent jejunal ulcer. Moore (1947)³⁶ described a patient who had evidence of marginal ulcer despite repeated resections for exclusion but when the antral mucosa was removed he recovered. Wangensteen and Linn (1942)³¹ called attention to the unsatisfactory clinical results after resection for exclusion if the antral mucosa is not removed. It is interesting that in Linn's (1945)⁹ series of experiments dogs with a Finsterer resection for exclusion in which three fourths of the stomach was removed, failed to develop ulcers after injections with histamine in beeswax whether or not the antral mucosa was removed. However in the hands of Pearce and Schilling (1947)³⁰ 90 per cent of their dogs which had a two thirds gastric resection with the pyloric antrum left intact developed jejunal ulcer after histamine injections but only 2 per cent of dogs with the same resection with removal of the pylorus developed histamine induced ulcers.

Removal of a triangular portion of the stomach from the greater curvature side or fundusectomy was proposed by Connell (1929-1932)^{32, 33} because he felt that such a procedure carried an insignificant risk and still removed a considerable amount of acid producing tissue. However his quoted mortality rate was 14.3 per cent and one recurrence occurred in fourteen cases. His experimental work on dogs indicated that while the gastric acidity was considerably reduced soon after the operation it later returned to normal values. Watson (1933)³⁴ as well as Seely and Zollner (1935)³⁵ also noted that after such procedures in dogs the reduction in acidity was only temporary. Strangely enough Fauley and Ivy (1936)³⁶ found that such a procedure prevented ulcer formation in a considerable number of their Mann-Williamson dogs and Linn (1945)² observed that although fundusectomy alone failed to prevent histamine induced ulcers fundusectomy combined with gastrojejunostomy appeared to furnish protection against the histamine induced ulcer. This combination of fundusectomy and gastrojejunostomy has been performed in eight patients in Wangensteen's clinic³⁷. Although achlorhydria was achieved in only two of these patients no postoperative jejunal ulcers were reported in the follow up study.

Believing that neutralization of acid by reabsorption of intestinal juices was the chief factor of success in any operation designed to ablate the ulcer diathesis by lowering the gastric acidity Devine (1923)³⁸ recommended a pyloric exclusion with gastroenterostomy without removal of any portion of the stomach. Such a procedure was modified by Binnert (1932)³ to include removal of the antral mucosa. However all the experimental evidence indicates that this procedure is of little value. Crindley (1941)³⁹ noted an increase in the gastric acidity in dogs after such a procedure. In attempting to devise a method of cholecystogastrostomy which would prevent cholangitis Sandblom and his colleagues (1936)⁴⁰ and Centile (1935)⁴¹ performed such a procedure in conjunction with anastomosis of the gall bladder to the excluded antrum and

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or opposite the stoma. They most frequently occur in patients who show evidence of high gastric acidity^{1, 2, 3, 4} and are quite rare in patients with achlorhydria although such cases have been reported.^{14, 15} Graham and Lewis (1931)¹⁶ felt that the gastric analyses in such reported cases might be open to criticism perhaps on the grounds that the position of the tube was not ascertained radiographically. Likewise jejunal ulcers are extremely rare after resection for gastric ulcer.^{1, 4, 17} Although Ransom (1947)⁴¹³ reports an incidence of 3 per cent after such operations. This fact must be taken into consideration in evaluating reports of the incidence of jejunal ulcer in mixed series of operations for gastric and duodenal ulcer. Jejunal ulcer almost never occurs after resection for gastric carcinoma^{17, 2, 18} although Judd¹⁹ and St John's group⁴²¹ each reported such a case. Ninety per cent of postoperative jejunal ulcers occur in men and they most frequently occur in the third or fourth decade.^{20, 2}

The Cause of Jejunal Ulcer

In a discussion of the etiology of postoperative jejunal ulcer, all of the factors concerned in the ulcer diathesis as outlined in the section on etiology of peptic ulcer must be given consideration and all of these factors have had their champions. Mayo (1910)³¹⁶ Poole (1917)⁴¹¹ Bastedo (1920)³⁹ Benedict (1933)⁴ and many others attributed the development of jejunal ulcers after gastroenterostomy to the use of nonabsorbable sutures since such sutures are sometimes noted in the base of these ulcers or to the traumatic effect of clamps applied to the gut during the operative procedure. However, Judd and Hoerner (1935)³⁶⁰ and Lewisohn (1921)² found that there was no change in the incidence of jejunal ulcer after gastroenterostomy when catgut was used exclusively. Montgomery (1923)⁶ observed that the jejunal ulcers which occurred after gastroenterostomy in his dogs had no relation to the use of nonabsorbable sutures and that the ulcers did not occur at the site of the clamps used during the operative procedure. Likewise Scott (1929)⁴⁴ found that the ulcers in his Mann-Williamson dogs in which the anastomoses were made with silk did not occur at the anastomosis or in relationship to the silk sutures. Callagher (1927)¹⁶⁸¹⁶⁹ noted in dogs that acute lesions made by clamps in the mucosa of the jejunum either in situ or transplanted into the stomach healed quite rapidly even when hydrochloric acid was injected into the stomachs of the animals.

Jejunal ulcer after gastric resection was ascribed by Birgfeld (1925)⁴³ to a triad of spasm, stasis and hyperacidity. Stemberg and Starr (1934)⁴⁶⁸ recorded that when they did an Fxalto short circuiting procedure (deviating the duodenal contents to the ileum) in dogs and in addition stripped the circular and longitudinal muscle fibers from the jejunum except at the mesenteric border no ulcers occurred in the regions from which the muscle had been stripped. Moreover they repeated the experiments of Matthews and Dragstedt (1932)³³⁴ anastomosing the ileum to a J-vagov pouch but stripping off the ileal musculature as before and found that no ulcers developed in six dogs prepared in this fashion. They theorized that when acid entering the intestinal segment was too highly concentrated the intestinal muscles contracted to hold it back thus spasm

observed an incidence of jejunal ulcer in their dogs of 35 and 24 per cent, respectively. Linnin's work (1945)²² indicated that this pyloric exclusion operation failed to prevent histamine induced jejunal ulcers. Graham (1938)²³ observed jejunal ulcers in three of four patients with such procedures.

Many years ago an enteroenterostomy between the afferent and efferent jejunal loops was recommended by Braun (1892)²⁴ as an adjunct to gastroenterostomy to avoid stagnation in the proximal loop. This has since been utilized in conjunction with gastric resection,²⁵ but it has been recorded by Walters (1936)²⁶ that there is less reduction of acidity when such an enteroenterostomy is added to gastric resection than with an ordinary resection alone, and clinically such a procedure predisposes to the development of jejunal ulcer.²⁷ As Luby (1940)²⁸ has so wisely observed "Any operation by which the alkaline jejunal contents are prevented from going back into the stomach to lower acidity predisposes to the occurrence of a gastrojejunal ulcer. Such an observation is strengthened by the evidence . . .²⁹ that the Roux-Y anastomosis in conjunction with gastroenterostomy or gastric resection predisposes to jejunal ulcer. The disappointing results of the Schindler's procedure (total intragastric regurgitation of duodenal contents) apparently due to a prolongation of the gastric phase of acid secretion have already been noted.



JEJUNAL ULCER

General Observations

Throughout the literature the terms 'marginal ulcer', 'stomal ulcer', 'gastrojejunal ulcer' and 'jejunal ulcer' are used more or less synonymously. Hutchison (1919)³⁰ believed that the ulcers indicated by these terms included two varieties: the true jejunal ulcer which he thought due to hyperacidity and the anastomotic ulcer, which he thought due to nonabsorbible suture material. Walton (1925)³¹ felt that all of these ulcers started from the anastomosis. Even though this might not be evident in the resected specimen, Graham and Lewis (1935)³² recorded that only one in their series of forty-three 'marginal' ulcers was at the stomal suture line; all the others involved the jejunum only. The work of Ginzburg and Wile (1938)³³ indicated that at least 50 per cent of these postoperative ulcers involved the jejunum only and most of these occurred in the efferent loop. When one considers the fact that by far the greater majority of experimentally produced postoperative ulcers are in the jejunum presenting an intervening area of relatively normal jejunal mucosa (vide supra) it seems rational to refer to these ulcers by the more accurate term of 'jejunal ulcer'.

Primary benign jejunal ulcer is exceedingly rare³⁴ and jejunal ulcer seems to occur usually when unprotected jejunal mucosa is bathed by acid gastric juice as a result of some operative procedure such as gastroenterostomy or a variant of the Billroth II type of gastric resection. These ulcers are usually single, usually smaller than the ordinary peptic ulcer and usually situated on the anterior surface of the jejunum close to the anastomosis.³⁵ Like the ulcers found in Mann-Williamson dogs, they are more frequent in the efferent loop.

Graham (1938)¹⁷⁹ performed an extensive resection with a postcolic Polya type of anastomosis but used a long afferent loop in order to avoid postoperative mechanical obstructive difficulties. With such a long loop procedure, in a series of 140 resections for duodenal ulcer, he reported 4 jejunal ulcers, an incidence of 2.9 per cent but called attention to the fact that 3 of the 4 developed after limited resections only 1 occurring after a truly radical resection. Church and Hinton (1942)¹⁸⁰ followed a series of 104 patients who had gastric resections for ulcer, the length of follow up time averaging 2.8 years. Eighty-five per cent of these patients were operated upon for duodenal ulcer and some of them had had the operations in other clinics. These authors found that none of their own patients who had a two thirds resection and a long loop antecolic anastomosis developed proved jejunal ulcer, although 4 had clinical symptoms arousing the suspicion of the presence of such an ulcer. However, 2 patients in this group who had had limited resections elsewhere developed jejunal ulcer.

Recently King (1946)¹⁸¹ reported 75 consecutive resections of two thirds of the stomach for ulcer, with an antecolic long loop Hofmeister anastomosis, with only one recurrence (1.3 per cent). He too failed to indicate the site of the ulcer for which operation was indicated or the length of the follow up period. Kennedy and Reynolds (1946)¹⁸² took issue with the thesis that a short afferent loop is important in reporting 90 subtotal resections including 21 for gastric ulcer, 1 for jejunal ulcer, and 68 for duodenal ulcer, without a single recurrence these operations having been accompanied by an antecolic anastomosis with the stoma located 30 to 40 cm from the ligament of Treitz. While they indicated that some of these patients had been followed five years the length of follow up in the remainder was not stated. An incidence of 1.8 per cent jejunal ulcers after subtotal resection for ulcer with a long loop antecolic anastomosis has been recently reported by Bruusgaard (1948)¹⁸³. He noted however that the follow up period ranged from one to four years and felt that the incidence might increase with time. He also thought that his results would perhaps be improved if he used a shorter afferent loop.

THE RATIONALE OF THE SHORT AFFERENT JEJUNAL LOOP

On the clinical side it is apparent that the evidence is somewhat conflicting as to whether or not a short loop anastomosis is the most desirable in the prevention of jejunal ulcer after gastric resection. The experimental evidence is much more convincing. In 1945 the University of Minnesota group (1945)¹⁸⁴ reported some experiments with dogs which present indications that the length of the afferent loop is an important factor in the development of jejunal ulcer. Two series of dogs were prepared by performing a subtotal (three fourths) gastric resection making an end to side Hofmeister gastrojejunal anastomosis. In the first series of eleven dogs this anastomosis was performed as close to the closed end of the duodenal stump as was feasible the distance from stoma to stump varying from 12 to 15 cm. After a rest period of three months these dogs were injected daily with the histamine in beeswax mixture, receiving 30 mg of histamine base each day and after forty to forty five daily injections were sacrificed. Not a single jejunal ulcer was noted in this series of dogs, although

incidence of 2.5 per cent jejunal ulcer was reported by Walters, Lewis, and Lemon (1940)²⁹² in a series of 197 adequately followed gastric resections for duodenal ulcer, with short afferent loop postcolic anastomosis. Allen and Welch (1942-1946),²⁹³ who do a similar type of short loop procedure, in 1942 reported no jejunal ulcers in a series of 71 resections for duodenal ulcer, but in 1946 in a series of 129 resections for duodenal ulcer, they reported 3 jejunal ulcers an incidence of 2.3 per cent, in addition there were 3 patients who had severe gastrointestinal bleeding, and 3 others who had pain sufficiently severe so that they were classed as poor results. If these 6 patients were assigned a presumptive diagnosis of jejunal ulcer, the incidence in Allen and Welch's later series would then be 7 per cent. Baker (1946),²⁹⁴ utilizing a posterior short loop anastomosis reported that no jejunal ulcers had occurred in his series of 105 resections for ulcer. In an analysis of 3 patients with jejunal ulcer, who had had their primary operations elsewhere, he felt that the chief factor involved was an afferent loop that was too long, stating "..... the shorter the proximal loop that is anastomosed, the greater the concentration of alkaline bile and pancreatic juices to bathe and protect the anastomosis."

At the Lahey Clinic an extensive (three fourths to four fifths) resection of the stomach for ulcer is practiced combined with an antecolic long loop Hofmeister anastomosis²⁹¹ with the stoma twelve to sixteen inches past the ligament of Treitz. Lahey^{291, 292} although admitting that the incidence of jejunal ulcer is probably lower after a short loop postcolic anastomosis, has consistently advocated the antecolic long loop anastomosis because of (1) the greater ease of the technical procedure, (2) the diminished likelihood of involvement of the blood supply of the transverse colon if a jejunal ulcer should develop and the diminished likelihood of gastrojejunal fistula and (3) the relative ease with which a jejunal ulcer can be handled surgically, if it should develop after an antecolic anastomosis as compared with the technical difficulty and hazards involved in surgical interference with a jejunal ulcer developing after a postcolic anastomosis. Of course, if, as Wangensteen believes, the incidence of jejunal ulcer after the short loop anastomosis can be reduced to an almost negligible fraction of a per cent this argument would no longer be tenable. Lahey (1945)²⁹² stated that the average incidence of jejunal ulcer after gastric resection is 2 to 3 per cent but the figures recorded from his clinic are higher than this. In 1937, Marshall and Kiefer²⁹¹ reported 5 jejunal ulcers in a series of 74 resections with antecolic anastomoses an incidence of 6.7 per cent. In 1940 Kiefer²⁹¹ reported that while 49 patients with a similar type of procedure done for gastric ulcer did not develop jejunal ulcer, in 173 patients with the same procedure done for duodenal or jejunal ulcer there were 6 (3.4 per cent) jejunal ulcers proved at a later operation and 6 others with an x-ray diagnosis of jejunal ulcer, a total incidence of 6.8 per cent. However as Wangensteen (1944)²⁹⁶ pointed out if another 8 patients who had upper gastrointestinal hemorrhage after such a procedure but failed to show evidence of jejunal ulcer on x-ray examination could be presumed to have jejunal ulcers the incidence for the series of 173 cases would then be 11.6 per cent and the incidence in the mixed series of 222 cases would be 9.0 per cent.

tions were due to their use of duodenojejunal loops which varied considerably in length neutralization was thought to be more complete when a short loop was used

In his advocacy of the short afferent jejunal loop Wangenstein (1942-1947)^{20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100} maintained that with such a short loop neutralization of the remaining gastric acidity is improved as compared with that after a long loop procedure, because of three factors. These are (1) the secretin factor (2) the spatial separation between the biliary and pancreatic ducts and the gastrojejunal stomach, and (3) the increasing sensitivity or susceptibility of lower segments of bowel to the digestive activity of gastric juice. Each of these factors will be discussed in detail. A fourth factor enterogastrone has been entertained by Kolouch (1946)² but dismissed because of the fact that enterogastrone has been located in all segments of the bowel including the colon. In a series of extremely complicated experiments using the Schmilinsky procedure but varying it in a number of ways by employing various lengths of bowel various types of anastomosis and interposing various segments of gut Wangenstein's group (1945)²⁴⁰ has attempted to evaluate the relative importance of these three aforementioned factors. Their attempts to separate the three factors were not entirely successful and their conclusions from these experiments were somewhat uncertain although they felt that the "sensitivity" factor had less importance than the other two. The operations were so complicated, so many variables were introduced and the series of dogs (two for each type of operation) were so small that this work lacks definitive significance.

~~4~~ The Secretin Factor

The importance of the pancreatic juice as an agent capable of neutralizing buffering and diluting hydrochloric acid has already been emphasized. The vagus nerve is thought to be the secretory nerve of the pancreas.⁴¹ However bilateral transthoracic vagotomy in experimental animals does not have any marked influence on the volume of pancreatic juice obtained through a pancreatic fistula.⁴⁴ The hormonal mechanism of exocrine pancreatic secretion is more important. Dolinski⁴⁵ in 1894 discovered that an ingested solution of hydrochloric acid was an exceedingly strong stimulus of pancreatic secretion. According to Pavlov (1910)²⁹⁷ Popielski showed that hydrochloric acid activated pancreatic secretion only when it reached the duodenum and Wertheimer and Lepage found that this activity could be obtained from the duodenum jejunum and ileum (except for the last two feet) and that the effect diminished in intensity with descent in a caudal direction. They also showed that intravenous injection of hydrochloric acid had no effect on pancreatic secretion.

The experiments of Wertheimer and Lepage were repeated by Bayliss and Starling (1902)⁴⁴. The pancreatic duct was cannulated and a loop of jejunum isolated with section of all nerves to it to exclude the possibility of a reflex phenomenon. When acid was introduced into such a loop pancreatic secretion was stimulated. The jejunal mucosa was extracted and this extract when injected intravenously elicited a copious flow of pancreatic juice. The 'secretin theory' was thus elaborated by Bayliss and Starling. They thought that contact

two of them had superficial gastric erosions and one had a few small submucosal hemorrhages. In the second series of seven dogs the same operation was done except that the anastomosis was made at a distance from the inverted duodenal end varying between 27 and 78 cm. After the three month rest period, histamine in beeswax injections were given daily. Three of these dogs died at three, twelve and twenty two days, respectively, after the start of the injections of peritonitis secondary to perforated jejunal ulcers. Two of these three had the longest (78 cm) afferent loops. The remaining four dogs were sacrificed after either forty five or forty eight days of histamine injections and all showed large jejunal ulcers usually opposite the stoma. A third series of dogs received no histamine injections. Two of these had a hemigastrectomy with a long (78 cm) afferent duodenojejunal loop. One was sacrificed 210 days after the operative procedure and no ulcer found but the second dog died 120 days after the procedure of peritonitis secondary to a perforated jejunal ulcer. A third dog with a 60 per cent resection and an unusually long (144 cm) afferent loop died 338 days after the procedure of peritonitis secondary to a perforated jejunal ulcer. A fourth dog with a 75 per cent resection and an afferent loop 90 cm in length had at the time of publication survived 761 days after the procedure with no clinical evidence of ulcer.

The importance of the results in the last group of dogs may be minimized because the resections in three of them were small and the afferent loops were so ridiculously long that no clinical comparison is evident. However the importance of the results in the first two groups of dogs as well as the direct clinical application of these results is immediately obvious. If a three fourths gastric resection with a short afferent loop will protect dogs from histamine induced ulcers while a three fourths resection with a long afferent loop will not it would seem logical to assume that the former operation would be more satisfactory in ridding man of the ulcer diathesis.

The University of Minnesota group (1945)¹¹ has also demonstrated the importance of the short loop anastomosis by the use of the Schmilinsky procedure which has been discussed previously. In one series of eleven dogs, they excised the pylorus closing the duodenal stump and then sectioned the bowel 8 to 15 cm from the stump. The aboral end of the intestine was used to make an end to end gastroenterostomy while the oral end was anastomosed to the stomach above thus providing complete intragastric regurgitation of the duodenal contents. These dogs were sacrificed at intervals varying from 82 to 360 days after the procedure and only one of them was found to have developed a gastrojejunal ulcer. In a second series of six dogs the same operation was done except that the length of the duodenojejunal loop varied from 76 to 90 cm. These dogs became irritable and languid and died at intervals varying from 50 to 145 days after the procedure. Four of the six had perforated jejunal ulcers just distal to the efferent stoma while one other had a large gastric ulcer on the greater curvature of the fundus and the remaining dog had a severe gastritis with scattered pin point erosions. Thus it was thought that the variable results obtained with the Schmilinsky procedure by previous investiga-

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The Secretin Factor

The importance of the pancreatic juice as an agent capable of neutralizing, buffering, and diluting hydrochloric acid has already been emphasized. The vagus nerve is thought to be the secretory nerve of the pancreas⁴¹. However bilateral transthoracic vagotomy in experimental animals does not have any marked influence on the volume of pancreatic juice obtained through a pancreatic fistula⁴². The hormonal mechanism of exocrine pancreatic secretion is more important. Dolinski⁴³ in 1894 discovered that an ingested solution of hydrochloric acid was an exceedingly strong stimulus of pancreatic secretion. According to Pavlov (1910)³⁹ Popielski showed that hydrochloric acid activated pancreatic secretion only when it reached the duodenum and Wertheimer and Lepage found that this activity could be obtained from the duodenum jejunum and ileum (except for the last two feet) and that the effect diminished in intensity with descent in a caudal direction. They also showed that intravenous injection of hydrochloric acid had no effect on pancreatic secretion.

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of hydrochloric acid with the epithelial cells in the duodenum caused the production of a hormone "secretin," by a process of hydrolysis from a precursor, "prosecretin." Present in the cells, this secretin is absorbed into the blood stream and carried to the pancreas, where it acts specifically on the pancreatic cells, resulting in the production of pancreatic juice proportional in amount to the quantity of secretin in the blood.

✓ The experiments of Mellanby (1926)³³¹ indicated that the cholic acid present in bile would produce this secretin effect when introduced into the small intestine. Mellanby and Huggott (1926)³³² confirmed the work of Bayliss and Starling, except that they felt that it was proved by extraction with various substances, that secretin existed in the intestinal mucosa in the preformed state, and not as the precursor, prosecretin. While pancreatic juice obtained by them by vagal stimulation was rich in enzymes, and with prolonged vagal stimulation the pancreatic cells showed marked signs of exhaustion, the juice secreted in response to secretin was poor in enzymes but was secreted in copious quantities, and the pancreatic cells showed no signs of exhaustion after prolonged stimulation with secretin. No secretin was found in the gastric mucosa by these workers, but a considerable amount was found in the upper small intestine and only a slight amount in the lower small intestine and colon. Secretin has actually been isolated in the form of a crystalline picrolonate by Greengard and Ivy (1938)³³³ from the mucosa of the upper six feet of the dog's intestine and a quantitative response to the intravenous administration of this substance to dogs with pancreatic fistulas was determined by the same group (1941)³³⁷.

✓ Abundant experimental evidence has been cited by Pavlov (1910)³⁰⁷ indicating that acid extracts of the upper intestinal mucosa will excite the flow of bile. Puestow (1931)⁴¹¹ showed that bile was discharged into the duodenum shortly after acid chyme entered the small intestine. Although Pavlov felt that this excitosecretory effect was due to secretin as did Still, McBern and Ries (1931)⁴¹² in their work with dogs with biliary fistulas, Ivy (1929)⁴⁴⁴ after demonstrating by cross circulation experiments that when N/10 HCl, as well as various fats and oils were injected into the duodenum, something got into the blood stream which caused the gall bladder to contract, felt that this was a different hormone, and called it "cholecystokinin." More recently, Agren (1939)⁴ has shown that secretin and cholecystokinin are different, and has prepared each free from the other. The work of Delezenne and Frouin as reported by Pavlov (1910),³⁰⁷ indicated that weak solutions of hydrochloric acid

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type of procedure would result in a diminished secretion of these substances capable of neutralizing, buffering, and diluting the remaining gastric acid, and thus with a more aboral anastomosis the incidence of postoperative jejunal ulcer would be increased. An attempt to determine this point directly was made by Kolouch (1946, 1947)^{278, 279}. He provided dogs with pancreatic fistulas and after determining the pancreatic secretory response of each dog to a variety of enteral and parenteral stimuli, subtotal (three fourths) gastric resections were done. Two series of three dogs each were used. In one series, the afferent jejunal loop was short while in the other, it was long. The comparisons of the pancreatic secretion before and after these resections indicated that resection of the stomach caused a reduction in volume of the pancreatic secretion, and that this reduction was greater when a long afferent loop was used. However Kolouch admitted that these results must be taken with some reservation, because the secretory responses to various stimuli were rather inconstant both before and after gastric resection.

The Spatial Factor

It was felt by Wangensteen^{303, 306, 307} that the power of the pancreatic and biliary secretions and succuss entericus to neutralize, dilute, and buffer gastric acid would be diminished as the distance from their source to the gastrojejunal stoma increased.

Various studies of the acidity of the contents of the small intestine shed very little light on the subject. Mann and Bollman (1930)³ studied the secretions of the contents of various segments of the intestinal tract in dogs by the use of fistulas made from a loop of ileum anastomosed to the exterior and to the portion of bowel to be studied. They found that while the content of the duodenum might be acid when highly acid values were found in the stomach, the usual reaction of the small intestine contents was alkaline (pH 7.0 to 8.0), and after a meal was about pH 6.5 to 7.5. Robinson (1935)⁴¹⁹ found that the pH was about 6.5 in the duodenum in dogs and increased gradually in the aboral direction to about 7.5 or 8.0 at the ileocecal valve. He perfused segments of bowel from various levels with a number of different solutions, and found that regardless of the pH of the solution used the pH of the solution which returned was relatively constant. The progressive increase in pH throughout the jejunum was thought due to a combined increase in bicarbonate and decrease in CO_2 tension.⁴²⁰ Miller and Karr (1936)³⁴³ studied the reaction of the intestinal contents of man at various levels by intubation and found that the reaction of the jejunal contents was usually neutral, but when a strong stimulus to gastric secretion of acid such as histamine was administered a more acid intestinal reaction resulted. McGee and Hasting (1942)³⁴⁴ in similar intubation studies found that the reaction of the jejunal contents in man was slightly acid (pH 6.5) and when this value was changed by the introduction of acid or alkali it returned to the normal level fairly promptly.

In dogs Wu (1935)³³⁹ studied the reaction of the jejunal contents 5 to 10 cm below the ligament of Treitz by means of Mann fistulas and found that in the fasting state the pH at this point usually varied from 7.6 to 8.1 (with

extremes of 6.9 to 8.3), and after a meal varied from 7.0 to 7.8 (with extremes of 5.2 to 8.2). He then performed the Mann-Williamson surgical duodenal drainage procedure in these dogs, sectioning the jejunum a short distance above the fistula he had already created and after this procedure again made pH determinations. The acidity was found to be markedly increased the pH in a fasting state varying between 5.5 and 7.9 (with extremes of 2.4 to 8.3), and after feeding, varying from 5.2 to 6.9 (with extremes of 1.7 to 8.3). This work gave some quantitative indication of the neutralizing and buffering value of the duodenal juices at a point 5 to 10 cm below the ligament of Treitz.

The loss in titratable alkalinity of a solution similar in composition and buffering value to the pancreatic juice of a dog when perfused through intestinal loops of various lengths was determined by Kolouch (1946)¹⁸ in dogs. After excluding the duodenal juices by ligating the duodenum distal to the entrance of the pancreatic ducts, or by ligating the pancreatic and common bile ducts, loops of jejunum were isolated by ligating each end of the loop. One catheter was inserted in the proximal end of the loop and another in the distal end. 50 cc of the prepared solution of known alkalinity was dripped through the proximal catheter in a period of two hours and withdrawn from the distal catheter by gravity and suction. The volume of the solution withdrawn was measured and again titrated with 0.1 N HCl. It was found that the alkaline solution lost volume and a large quantity of its buffering capacity in its passage through the loop of intestine. When the solution was passed through long (35 to 49.5 cm) segments of gut the reduction in volume and buffering capacity was much greater than when it was passed through a short (10 cm) loop, thus supporting Wangensteen's thesis.

Weiss, Graves and Gurriaran (1932)¹⁹ varied the Schmilinsky procedure so that the duodenal contents were introduced into the stomach immediately adjacent to the efferent gastrojejunal stoma. Although McCann (1929)²⁰ obtained jejunal ulcers in 80 per cent of his dogs when the duodenal loop was anastomosed to the fundus, Weiss and his associates found that with their procedure not a single ulcer occurred in fourteen dogs. The spatial factor in such procedures was emphasized by Maier and Crossman (1935)²¹ who felt that, in the Schmilinsky procedure, when the duodenal loop was anastomosed to the fundus, a considerable portion of the alkalinity was lost for neutralization at the stoma. They felt that the acid values obtained in gastric analysis after gastric resection were overemphasized since the pH of the efferent jejunal loop should be the important consideration in relation to the development of jejunal ulcer and this pH is the result of the interaction of the gastric chyme and the alkaline contents of the afferent loop at the stoma. It should be recognized however that in experiments based on the Schmilinsky procedure the same conditions do not obtain as are found in the afferent loop after gastric resection because acid is constantly being secreted by the gastric mucosa and whether or not jejunal ulcers develop is not necessarily a result of the spatial separation of duodenal secretions from the efferent stoma.

The site of duodenal drainage in Mann-Williamson dogs was varied from close to the gastrojejunostomy stoma to the distal ileum by Gallagher and

Palmer (1932)¹⁷¹ They reported no relationship between the site of drainage and the incidence or rapidity of ulcer formation. Wilhelmj, O'Brien and McCarthy (1936)²²⁹ repeated the Mann-Williamson procedure with the duodenum drained into the jejunum only a short distance below the gastrojejunal anastomosis. In four dogs no ulcers occurred and the regurgitation of the duodenal contents to the stomach was indicated by the presence of bile in the stomach. Thus it would appear that the distance separating the source of the duodenal secretions from the gastrojejunostomy stoma may have some importance in jejunal ulcer prevention.

The Sensitivity Factor

There is a considerable amount of evidence available indicating that the lower segments of small bowel are more susceptible to the digestive activity of gastric juice. The frequency of ulcer formation in the mucosa of the ileum adjacent to a Meckel's diverticulum when that diverticulum contains actively secreting gastric mucosa has been pointed out by Aschner and Karcilitz (1930),²³ and Lindau and Wulff (1931).³¹⁰ Kogut and Stein (1936)²⁴ collected from the literature a series of thirteen cases in which unintentional gastroileostomy had been done and added three cases of their own noting that in these sixteen cases four patients developed gastroileal ulcers and another had a severe gastroileitis. De Takats and Mann (1927)¹¹² have noted in dogs that when an isolated segment of jejunum with its blood supply intact is opened up and transplanted into the gastric wall a number of these animals will develop ulcer in the transplanted jejunum especially if the transplantation is in the region of the lesser curvature.

Langeskiöld (1914)²⁹⁴ in acute experiments with dogs perfused segments of duodenum and jejunum with various solutions including natural gastric juice and dilute hydrochloric acid for various lengths of time and concluded on the basis of his results that the upper part of the duodenum was probably more resistant to gastric juice than the lower portion of the duodenum and jejunum. The work of Langeskiöld was recently repeated with modifications by Schiffman and Warren (1942)⁴⁴¹ who concluded that in the absence of the bile and pancreatic secretions the duodenum was more susceptible to acid alone than either the jejunum or ileum and that the susceptibility of the latter two was about equal. Matthews (1931)²³² found that in dogs he could consistently produce ulcers in the ileum by making an anastomosis between a Pylor pouch and a loop of ileum. Fauley and Ivy (1929-1931)⁴⁴⁶⁻²⁴⁸ varied the Mann-Williamson procedure by dividing the duodenum one inch distal to the pylorus after sectioning the jejunum twelve inches below the ligament of Treitz; the aboral end of the jejunum was anastomosed to the proximal end of the duodenum (the distal end being closed) and the oral end of the jejunum anastomosed to the terminal ileum. All of their dogs developed ulcers but in each case these ulcers were not in the one inch of duodenum adjacent to the pylorus but in the first portion of the anastomosed jejunum. They felt that this indicated that the mucosa of the jejunum was more susceptible to digestion by gastric juice than that of the duodenum.

The work of McMaster (1934)²⁴⁵ is of special interest in this connection. In dogs, he sectioned the stomach 1 cm proximal to the pylorus closing the distal end. The proximal end was used to make a gastroenterostomy, using various segments of bowel in various dogs. Of 4 dogs with gastroduodenostomy, no ulcers developed, of 11 dogs with gastrojejunostomy, 5 (45.4 per cent) developed jejunal ulcers distal to the anastomosis, of 10 dogs with gastroileostomy, 7 (70 per cent) developed ileal ulcers just distal to the anastomosis. This work seemed to indicate not only that there was an aboral gradient of increasing susceptibility of the intestinal mucosa to digestion by acid gastric juice, but it may have also suggested the importance of the spatial separation of the duodenal secretions from the anastomosis.

Fistulas of the Mann type to the stomachs of dogs using loops of ileum, were made by Goldberg (1932),²⁴⁷ and when the portions of stomachs containing the fistulas were later converted to pouches, each dog developed an ulcer in the ileal segment and many of the ulcers perforated. Goldberg's work was continued by Harper (1932-1935)^{248, 249} using different segments of bowel to fashion the fistulas. He reported that when the duodenum was used for the fistula, ulcers formed but did not perforate, when the jejunum was used, the average life of the dogs before they died of perforated jejunal ulcer was 71 days and when the ileum was used, the average life before perforation was 23 days. This seemed to indicate an increasing vulnerability of the lower segments of small bowel to gastric juice. Using the hog as an experimental animal, Florey's group (1939)²⁵⁰ performed somewhat similar experiments and failed to obtain ulcers when the duodenum was used to fashion the fistula between the Pavlov pouch and body wall, but obtained ulcers in every animal in which the ileum was employed.

Driver, Chappell and Carmichael (1945)¹² in acute experiments resembling those of Langeskiöld perfused loops of the dog's jejunum at different levels with varying strengths of pepsin dissolved in N/10 HCl, varying the length of time of perfusion from four to thirty hours. They too found that the more distal loops of jejunum were more susceptible to the action of the acid peptic mixture than the more proximal loops and therefore felt that gastrojejunal

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of bowel from stomach to colon, to a drip of acid pepsin mixtures buffered to a pH equal to that of gastric juice and found that while the gastric mucosa was quite resistant to the corrosive action of these mixtures, the susceptibility of the mucosa of the duodenum, jejunum, ileum and colon to the acid peptic digestion was about equal.

In summary, then, while it is not entirely clear as to whether the secretin factor, the spatial factor or the sensitivity factor is the most important, there

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SUMMARY

A review of recent literature dealing with certain important physiologic aspects of gastric surgery, as well as with theories of ulcer causation, has been presented, indicating the long term results which may be expected from various operations with particular regard to subtotal gastric resection, and the type of gastric resection which should be most preferable.

CONCLUSIONS

1 Physiologic and anatomic studies to date indicate that the pyloric antrum secretes little or no hydrochloric acid. The hormonal or "gastrin" theory of gastric secretion has been fairly well substantiated although there is some difference of opinion concerning this among physiologists. At any rate, better clinical results are obtained when the pyloric mucosa is removed than when it is left in place. The weight of evidence indicates that gastric juice is secreted at a constant degree of acidity (0.5 per cent or 16 N HCl) and that the gastric acidity is lowered by the normal progress of regurgitation of alkaline duodenal contents. An operation for ulcer which is physiologically justifiable should provide for such a process of neutralization.

2 From the available evidence, it would appear that subtotal gastric resection offers the best long term results of any operation in use at present in the elective surgical treatment of benign gastric and duodenal ulcer. The procedure of choice appears to be a resection of three fourths or more of the stomach, including the pyloric mucosa with a Hofmeister type of gastrojejunal anastomosis made as close as is technically possible to the duodenum. The procedure of vagotomy appears to be promising in selected cases but its permanent place in ulcer surgery remains to be evaluated.

REFERENCES

- 1 Abell I. The present status of gastrectomy. *Am J Digest Dis* 7: 493-498, 1940.
- 2 Agren G. On the preparation of cholecystokinin. *Skand Arch Physiol* 81: 231, 1939.
- 3 Allen, A. W. Surgical treatment of duodenal ulcer. *Arch Surg* 44: 501-519, 1941.
- 4 Allen, A. W. Gastric ulcer and cancer. *Surgery* 17: 730-734, 1943.
- 5 Allen, A. W. and Welch, C. E. Gastric resection for duodenal ulcer—Follow up studies. *Ann Surg* 115: 530-543, 1942.
- 6 Allen, A. W. and Welch, C. E. Subtotal gastrectomy for duodenal ulcer. *Ann Surg* 124: 688-707, 1946.
- 7 Alley, A. The inhibitory effect of histamine on gastric secretion. *Am J Dig Dis and Nutr* 1: 787-794, 1935.
- 8 Alvarez W. C. Light from the laboratory and the clinic on the causes of peptic ulcer. *Am J Surg* 18: 207-231, 1932.
- 9 Alvarez W. C. What value has gastric analysis? *Gastro-enterology* 1: 534-536, 1943.
- 10 Alvarez W. C., Hosoi, J., Overgard, A. and Ascanio, H. The effects of degenerative section of the vagi and the splanchnics on the digestive tract. *Am. J. Physiol* 90: 631-633, 1929.
- 11 Anderson, A. C., Slotzky, B. and Moertz, R. W. Effect on gastric secretion of pedicle jejunal grafts in the wall of the stomach. *Gastroenterology* 4: 323-331, 1945.
- 12 Andresen, A. E. I. Results of treatment of massive gastric hemorrhage. *Am. J. Dig Dis* 6: 641-646, 1939.
- 13 Antru, W. D., Lord, J. W. and Stefko, P. Comparative effects of gastroenterostomy and pedicle jejunal graft on the pH of gastric mucosa. *Proc Soc Exp Biol and Med* 52: 99-100, 1943.
- 14 Antru, W. D., Lord, J. W. and Stefko, P. Effects of pedicle grafts of jejunum in the wall of the stomach on gastric secretion—Experimental and Clinical studies. *Ann Surg* 118: 490-522, 1943.

- 15 Andriani W D R J J C S - - -
- 16 Andriani W D R J J C S - - -
- 17 Apperly E I Duodenal regurgitation and the control of the pylorus, Brit J Exper Path 7 111 119, 1926
- 18 Apperly E I and Norris J H The automatic regulation of gastric acidity J Physiol 70 159 168 1926
- 19 Aschner I W and Karelitz S Peptic ulcer of Meckel's diverticulum and ileum Ann Surg 91 573 582 1930
- 20 Aschoff I Lecture in pathology pp 203 212 Paul P Hoeber Inc 1925
- 21 Babkin B I The physiological factors determining the acidity of the gastric juice and of the gastric contents (Ann) M A J 17 30-42, 1947
- 22 Babkin B I The acidity of the gastric juice Am J Surg 7 498 504 1929
- 23 Babkin B I The chemical phase of gastric secretion and its regulation, Am J Dig Dis & Nutr 1 110 71 1934
- 24 Babkin B I The abnormal functioning of the gastric secretory mechanism as a possible factor in the pathogenesis of peptic ulcer (Ann) M A J 38 43-49 1944
- 25 Babkin B I The triple mechanism of the chemical phase of gastric secretion Am J Dig Dis 5 467 471 1938
- 26 Babkin B I Secretory mechanism of the digestive gland Paul P Hoeber Inc 1944
- 27 Beckrich W H, Schmitt, C R, and Benzell J M The relation of bile and pancreatic juice to duodenal ulcer in dog Proc Soc Exper Biol & Med 40 3 1944
- 28 Baggio G L'influenza che sulla produzione dell'ulcera del digiuno viene esercitata dalla deviazione del contenuto duodenale Ann. Ital. Pat. Clin 3 553 1944
- 29 Baggio G Experimental gastric ulcer from obstruction to the emptying of the stomach International Abstract of Surgery 41 490 1927
- 30 Baker I W Gastrojejunal ulcer following gastric resection West J Surg 54 341 342 1946
- 31 Balfour, D C The occurrence and management of gastrojejunal ulcer, Ann Surg 84 71 236 1926
- 32 Bancroft Fred W A modification of the Devine operation of pyloric exclusion for duodenal ulcer Am J Surg 16 231 234 1937
- 33 Baritell A Perforated gastroduodenal ulcer Surgery 21 247 1947
- 34 Baronofsky J Portal hypertension and the ulcer diathesis Proc Am Fed Clin Res 2 Oct 1945
- 35 Baronofsky I and Wangensteen O H Bilroth II laparotomy provoked ulcer production of erosion or perforation of small amounts of acid in the rabbit
- 36 Baronofsky I and Wangensteen O H Proton ulcer (gastric and/or duodenal) experimentally produced through the agency of chronic arterial spasm invoked by the intramuscular implantation of epinephrine or pituitrin in beeswax Bull Am Coll Surg 30 59 60 1945
- 37 Bartels P N and Dahn J W Gastric resection for peptic ulcer Surgery 21 496 511 1944
- 38 Baronofsky I and Wangensteen O H The need of surgery in peptic ulcer with remarks on the role of the vagus nerve in the regulation of gastric secretion and on the influence of the vagus nerve on the production of ulcers peptiques expérimentaux et cliniques 3 1067 1068 1935
- 39 Baxter B C Nervous control of the pancreatic secretion in the rabbit Am J Physiol 96 349 351 1931
- 40 Baxter B C Influence of splanchnic nerves on gastric secretion Proc Soc Exper Biol & Med 29 511 512 1932
- 41 Baxter B C Role of the sympathetic nervous system in gastric secretion Am J Dig Dis & Nutr 1 40 42 1934
- 42 Baylis W M and Starling P H The mechanism of pancreatic secretion J Physiol 99 3 190 190
- 43 Beaumont W The effect of the vagus nerve on the secretion of the pancreas after section of the vagus nerve after section of the vagus nerve
- 44 Beaumont W The effect of the vagus nerve on the secretion of the pancreas after section of the vagus nerve after section of the vagus nerve

- 41 Benechet E B Jejunal ulcer—An analysis of 36 cases and study of the literature Surg Gyn & Obst 56 807 919 1933
- 42 Berg A A The radical operative cure of gastric and duodenal ulcer S Clin N America 8 1117 1191 1925
- 43 Berg A A The mortality and late results of subtotal gastrectomy for the radical cure of gastric and duodenal ulcer Ann Surg 92 340 361 1930
- 44 Berg B N Peptic ulcers—comparative frequency after deprivation of bile and pancreatic juice Arch Surg 28 1057 1061 1934
- 45 Berg B N Gastric ulcers produced experimentally by vascular ligation Arch Surg 54 556 1917
- 46 Berg B N and Jelling J W Biliary and hepatic factor in peptic ulcers Arch Surg 20 997 1015, 1930
- 47 Berg B N and Jelling J W Duodenal and gastric ulcers in dogs with resection of peptic ulcers after deprivation of bile and pancreatic juice Expt Biol & Med 30 303 312 1929
- 48 Berg B N and Jelling J W The relation of the duodenum to the stomach A histopathologic study of the duodenum and its relation to the stomach Surg 4 84 94 1908
- 49 Berk J E Rehfu M E and Thomas J F The acidity of the ulcer bearing area of the duodenum in normal persons Am J Dig Dis 9 276 281 1942
- 50 Berk J E Thomas J E and Rehfu M E The effect of gastric hypersecretion on the reaction and neutralizing ability of the contents of the first part of the duodenum in normal dog Am J Dig Dis 9 297 301 1942
- 51 Berk J E Thomas J E and Rehfu M E The acid factor in duodenal ulcer as evaluated by the acidity and neutralizing ability in the duodenal bulb Am J Dig Dis 9 331 345 1942
- 52 Bert C H and McHenry F W Histamine Physiological Review 11 371 477 1931
- 53 Bert P R and Orator V The vagus nerve and its relation to peptic ulcer Ann Surg 96 184 191 1925
- 54 Bickel A Beobachtungen am Hunden mit exstirpiertem Duodenum Klin Wchnschr 46 1201 120 1909
- 55 Birgfeld E Ueber das Ulcus pepticum jejuni nach Magenresektion Arch f klin Chir 137 58 58 1925
- 56 Blackford J Massive gastric hemorrhage Am J Dig Dis 6 638 641 1939
- 57 Black E F Peptic ulcer—An experimental study Surg Gyn. and Obst 61 480 493 1935
- 58 Bloomfield A I The problem of gastric hyperacidity Am J Dig Dis & Nutr 6 700 702 1940
- 59 Bloomfield A I The indications for operation in cases of peptic ulcer from an internist's point of view Surgery 17 611 695 1945
- 60 Bloomfield A I and Keefer C S Clinical physiology of the stomach Simultaneous quantitative observation on gastric secretory volume acidity and motility Arch. Int Med 38 145 154 1941
- 61 Boerema J 1948
- 62 Bogota N 1948
- 63 Bolivier W 1948
- 64 Bolivier W 1948
- 65 Bolivier W 1948
- 66 Bolivier W 1948
- 67 Bolivier W 1948
- 68 Bolivier W 1948
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- 95 Bolivier W 1948
- 96 Bolivier W 1948
- 97 Bolivier W 1948
- 98 Bolivier W 1948
- 99 Bolivier W 1948
- 100 Bolivier W 1948

140 1923

- 86 Case J T Gastric and duodenal roentgen ray findings after operation J A M A 85 1385 1 29, 1947
- 87 Cheney, G Gastric acidity in chicks with experimental gastric ulcers Am J Dig Dis 5 104 107, 1934
- 88 Chlumsky V Weitere Erfahrungen ueber die Gastrostomie, Beitr z klin. Chir 27 331, 1900
- 89 Church, R E and Hinton J W The results of gastroenterostomy in gastric and duodenal ulcers—Report of 106 cases followed for an average of 71 years post operation J A M A 85 693 703 1927
- gastric resection for
Exper Biol & Med
Am J Physiol 137
- 91 Comfort M W clinical invest — —a review of
- 92 Connell F G duodenal ulcer gastric and
- 93 Connell F G 1930 3 636 652,
- 94 Connell F G Fundus resection—experimental Surg, Gynec, & Obst 53 750 759 1931
- 95 Connell F G I resection of the fundus of the stomach for peptic ulcer Ann Surg 96 200 203, 1932
- 96 Counseller, D S Waugh J M and Craggett, O T Report of surgery of the stomach and duodenum for 1943 Iro Staff Meet Mayo Clinic 19 544 550 1944
- 97 Crandell W B Boehm W F and Mulholland, J H Effects of supra diaphragmatic section of the vagus nerves in man Arch Surg 65 343 348 1947
- 100 Crile G W Recurrent hyperthyroidism, neurocirculatory asthenia and peptic ulcer Treatment by operations on the suprarenal sympathetic system J A M A 97 1616 1618 1931
- 101 Crile G Peptic ulcer South Surg 2 273 280 1930
- 102 Cushing, H
- 103 Custer M
- 104 Cut
- 105 Dwyer J Duodenal Dis & Nutr 2 501 504 1930
- 106 Denver J B and Reimann S P Subtotal gastrectomy J A M A 85 1619 1620 1947
- 107 DeBakey, M F Peptic ulceration—The relative protective value of the alkaline duodenal juices Arch Surg 34 230 241 1937
- 108 DeBakey M The physiology of peptic ulcer SCIENCE 2 653 674 1947
- 109 Denk W Studien ueber die Aetiologie und Prophylaxe des postoperativen jejunalen Geschwures Arch f klin Chir 116 152 1921
- 110 De Takats G The perverted physiology of the stomach after gastric operation Am J M Sci 172 45 51 1946
- 111 De Takats G The surgery of gastric and duodenal ulcers—Experience of the first surgical clinic University of Budapest Ann Surg 83 21 221 1946
- 112 De Takats G and Mann P C The effect on the jejunal mucosa of transplantation of the stomach in gastric surgery Surg Gyn. & Obst 85 693 703 1947
- trichloroacetic acid produced by an extra
- mal ulcer Quart J Exper Physiol

- 116 Dolnik I L Influence of acids on the secretion of the pancreatic gland, The 14, St. Petersburg 1894—Quoted by Bakkin (20)
- 117 Dragstedt L R Contributions to the physiology of the stomach XXXVIII Gastric juice in duodenal and gastric ulcers, J A M A 68 3:0 333, 1917
- 118 Dragstedt L R Some physiologic principles involved in the surgical treatment of gastric and duodenal ulcer Ann Surg 102 5:0 275 1935
- 119 Dragstedt L R Pathogenesis of gastroduodenal ulcer Arch Surg 44 438, 1942
- 120 Dragstedt L R Some physiologic problems in surgery of the pancreas, Ann Surg 118 576 589 1913
- 120a Dragstedt L R Vagotomy for gastroduodenal ulcer Ann Surg 122 973 989, 1945
- 121 Dragstedt L R and Ellis J C The fatal effect of the total loss of gastric juice Am J Physiol 93 407 416, 1929
- 121a Dragstedt L R Harper P U Torrey E B and Woodward E R Section of the vagus nerves to the stomach in the treatment of peptic ulcer Ann Surg 126 687 693 1947
- 122 Dragstedt L R and Owens F M Supradaphragmatic section of the vagus nerves in treatment of duodenal ulcer Proc Soc Exper Biol & Med 53 152 154, 1943
- 123 Dragstedt L R Palmer W L, Schafer, P W, and Hodges P C Supradaphragmatic section of the vagus nerves in the treatment of duodenal and gastric ulcers Gastroenterology 3 4:0 469 1944
- 124 Dragstedt L R and Schafer P W Removal of the vagus innervation of the stomach in gastroduodenal ulcer SURGERY 17 742 749, 1945
- 125 Dragstedt L R and Vaughan A M Gastric ulcer studies Arch Surg 8 791 810, 1924
- 126 Driver P L and Carmichael E B The effect of bile salts on the experimental production of ulcers in dog Am J Dig Dis 12 378 379 1945
- 127 Driver R L Chappell R H and Carmichael F B Effect of concentration of pepsin and the differential susceptibility of jejunal elements in experimental jejunal ulcers in the dog Am J Dig Dis 12 166 167 1945
- 128 Driver R L Chappell R H and Carmichael E B Effect of hydrostatic pressure on the experimental production of ulcers Am J Dig Dis 12 168 169 1945
- 129 Drury D R McMaister P D and Pons P Observations on some causes of gallstone formation III The relation of the reaction of the bile to experimental cholelithiasis J Exp Med 39 401 423 1924
- 130 Durante L The trophic element in the origin of gastric ulcer Surg Gyn & Obst 22 394 406 1916
- 131 Ekins J S The chemical mechanism of gastric secretion J Physiol 34 133 144 1906
- 132 Ekins J S and Tweedy M The natural channels of absorption evoking the chemical mechanism of gastric secretion, J Physiol 38 263 267 1908
- 133 Elman R Spontaneous peptic ulcers of the duodenum following the total loss of pancreatic juice J Clin Investigation 10 193 1931
- 134 Elman R Probable influence of pancreatic juice in the regulation of gastric acidity Arch Surg 16 1956 1965 1925
- 135 Elman R The behavior of gastric acidity in duodenal ulcer and pyloric obstruction before and after gastroenterotomy Surg Gyn and Obst 49 344 350 1929
- 136 Elman P and Fekert C T Neutralization of gastric acidity following pyloric closure Proc Soc Exper Biol & Med 30 1343 1344 1933
- 137 Elman P and Hartmann A F Spontaneous peptic ulcers of duodenum after continued loss of total pancreatic juice Arch Surg 23 1050 1040 1931
- 138 Elman P and MacLeod J W Studies on the neutralization of gastric acidity Ewald test meal and X ray (barium meal) studies in patients with duodenal ulcer gastrojejunostomy and gastric resection Am J Dig Dis & Nutr 2 21 26 1935
- 139 Elman R and McCaughan J M On the collection of the entire external secretion of the pancreas under sterile conditions and the fatal effect of total loss of pancreatic juice J Exper Med 45 561 570 1924
- 140 Elman R and Powlette A P The role of the pyloric sphincter in the behavior of gastric acidity Arch Surg 22 464 477 1931
- 141 Emery E S and Monroe R T Peptic ulcer—a study of 506 cases Arch Int Med 43 846 873 1919
- 142 Falck E and Zuckschwerdt C Die Freigabe der Magen-Saftsekretion nach Rektion des Antrum Pylorusteils des Magen Deutsche Zeitschrift für Chirurgie 232 290 1931
- 143 Fatermann G B Recurrent gastric ulcer and associated gastrojejunal ulcer in presence of constant gastric acidity M Clin North America 11 1971 1976 1928
- 144 Frost J A Black R M and Dockerty M B Primary non-specific ulcers of the small intestine SURGERY 23 185 200 1948

- 145 Exalto J Ulcus jejuni, nach Castro enterostomie Mitt a d Grenzgeb d Med u. Chir 23 13 1911
- 146 Fauley G B and Ivy A C Experimental jejunal ulcer Proc Soc Exp Biol & Med 27 182-48 1919
- 147 " " of the consistency
- 148 " " of jejunal ulcer
- 149 " " of jejunal ulcer
- 150 Fauley G B, Strauss H A and Ivy A C Studies on the effects of subtotal gastric resection in the dog Am J Surg 17 427-43 1912
- 151 Ferguson A N A cytological study of the regeneration of gastric glands following the experimental removal of large areas of mucosa Am J Anat 42 40-45 1918
- 152 Frazer J M T The development of surgery of the stomach Ann Surg 90 8 941 1919
- 153 Finney J M T and Harrahan F M The surgical treatment of duodenal ulcer and results over a 15 year period Ann Surg 90 917-19 1919
- 154 Finsterer H Surgical treatment of acute profuse gastric hemorrhage, Surg Gyn & Obst 69 291-98 1919
- 155 Finsterer H and Cunha E The surgical treatment of duodenal ulcer, Surg Gyn. & Obs 52 1010-1114 1911
- 156 Flood C A and Howe F I Experimental study, on the effect of histamine on the healing of gastric defects—artificial gastric ulcer, Surg Gyn & Obst 58 126-14 1914
- 157 Flood C A and Mullin C R Experimental peptic ulcer—The effect of surgical duodenal drainage upon dogs and the value of histamine in preventing ulcer Am J Dig Dis & Nutr 3 249-50 1936
- 158 Florey H W Jennings M A Jennings D A and O'Connor R C The reactions of the stomach to histamine J Pathol & Bact 49 101-113 1940
- 159 " " of the effect of secretion of histamine on the healing of gastric ulcers J Pathol & Bact 49 101-113 1940
- 160 Friesen S R Baronofsky I D and Wangenstein O H Benzalyl fails to protect against the histamine provoked ulcer Proc Soc Exp Biol & Med 63 25 1941
- 161 Friesen S R plate D Jaxer D E Figg W and Wangenstein O H Production of allergic gastric and duodenal edema which predisposes to the histamine provoked ulcer in dog Surg 23 161-174 1914
- 162 " " Relationship of gastric acidity to peptic ulcers and the effect of histamine on the healing of gastric ulcers J Pathol & Bact 49 101-113 1940
- 163 " " of the effect of secretion of histamine on the healing of gastric ulcers J Pathol & Bact 49 101-113 1940
- 164 Friedman J C and Hamburger W W Experimental chronic gastric ulcer J A M A 63 341-344 1914
- 165 Friesen S R Baronofsky I D and Wangenstein O H Benzalyl fails to protect against the histamine provoked ulcer Proc Soc Exp Biol & Med 63 25 1941
- 166 Friesen S R plate D Jaxer D E Figg W and Wangenstein O H Production of allergic gastric and duodenal edema which predisposes to the histamine provoked ulcer in dog Surg 23 161-174 1914
- 167 " " Relationship of gastric acidity to peptic ulcers and the effect of histamine on the healing of gastric ulcers J Pathol & Bact 49 101-113 1940
- 168 " " of the effect of secretion of histamine on the healing of gastric ulcers J Pathol & Bact 49 101-113 1940
- 169 " " of the effect of secretion of histamine on the healing of gastric ulcers J Pathol & Bact 49 101-113 1940
- 170 " " of the effect of secretion of histamine on the healing of gastric ulcers J Pathol & Bact 49 101-113 1940
- 171 " " of the effect of secretion of histamine on the healing of gastric ulcers J Pathol & Bact 49 101-113 1940
- 172 " " of the effect of secretion of histamine on the healing of gastric ulcers J Pathol & Bact 49 101-113 1940
- 173 Gama G McHenry L J Physiol 79 233-238 1913
- 174 Gaviger D Clinical investigation and evaluation of the conservatively operated cases of peptic ulcer Bull. Staff Meeting Univ. of Minn. 19 81-110 1941

- 239 Ivy A C Studies on the secretion of the pyloric end of the stomach Am J Physiol 49 142 143, 1919
- 240 Ivy, A C Studies on gastric and duodenal ulcer J A M A 75 3540 1942 1920
- 241 Ivy, A C Contributions to the physiology of the stomach—LII Studies on gastric ulcer Arch Int Med 25 631 1920
- 242 Ivy A C A hormone mechanism for gall bladder contraction and evacuation, Am. J Surg 7 450-499 1949
- 243 Ivy, A. C The mechanisms of gastric secretion, SURGERY 10 861 878 1941
- 244 Ivy A C The prevention of recurrence of 'peptic ulcer' An experimental study Gastroenterology 3 443 449, 1944
- 245 Ivy A C The problem of peptic ulcer J A M A 132 1003 1009 1940
- 246 Ivy A C Droegemueller E H and Meyer J L Effect of experimental pyloric stenosis on gastric secretion Arch Int Med 40 434 440 1927
- 247 Ivy, A C, and Farrell, J I Contributions to the physiology of gastric secretion—VIII The proof of a humoral mechanism—A new procedure for the study of f r
- 248 Ivy 1931
- 249 Ivy A C Lim R K S, and McCarthy J E Contributions to the physiology of gastric secretion—II The intestinal phase of gastric secretion Quart J Exp Physiol 15 50 68 1920
- 250 Ivy A C Lim P K S and McCarthy J E Contributions to the physiology of gastric secretion—III An attempt to prove that a humoral mechanism is concerned in gastric secretion by blood transfusion and cross circulation Am. J Physiol 74 616 638 1920
- 251 Ivy A C and McIlvain G L The excitation of gastric secretion by application of substances to the duodenal and jejunal mucosa Am J Physiol 63 418 419 1923
- 252 Ivy A C and Oyama Y Studies on the secretion of pars pylorica gastrici, Am J Physiol 57 51 60 1921
- 253 Ivy A C Schrager V L and Morgan J E Spontaneous duodenal ulcers in dogs with chronic mild icterus and hepatitis, Proc Soc Exp Biol & Med 30 698 700 1932
- 254 Ivy A C and Whitlow J E The gastrin theory put to physiological test, Am. J Physiol 60 5 9 589 1920
- 255 Jenkins H P and Palmer W L Studies on experimental jejunal ulcer Proc Soc Exp Biol & Med 28 932 936 1931
- 256 Jones K H A simultaneously reted
- 257 Judd E S Jeju
- 258 Judd E S Jr Coll
- 259 Judd E S and the duodenum
- 260 Judd E S and
- 261 Kaplow H the intestine
- 262 Katzstein M Beitrag zur Entstehung des Magengeschwurs Arch f klin Chir 100 9 1961 191
- 263 Keeton P W and Koch F C The distribution of gastrin in the body Am J Physiol 37 4 1504 1910
- 264 Kehre I K W
- 265 Kell
- 266 Ken
- 267 Kennedy C S Revnoll R P and Cantor M O A study of the gastric tone after partial gastrectomy—An analysis of ninety gastric resections SURGERY 22 414, 1947
- 268 Kennedy C S Revnoll R P and Cantor M O Demonstration at operation of sphincter contraction during intragastric distention Surg 74 804 810 1947
- 269 Keppich h chloroanesthetized (erste Mit 48 118 122 1921
- 270 Kevala of duodenal contents on intragastric activity Surgery 14 3 508, 1943

- 373 Matthes W B Production of intestinal ulcers by active gastric juice, *Proc Soc Exp Biol & Med* 28 960 961, 1931

227 229, 1910

- 737 McCann J C Studies on the control of the acidity of the gastric juice Am. J Physiol. 89 483-496, 1929

- 410 McMaster, Paul L. Effects of diverting the gastric contents to the lower intestinal levels. *Arch Surg* 28: 825-836 1934

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47 n. & Obs.

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11

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- 358 1911 The effect of v.otomy on gastric emptying time, Am

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92 15

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- 358 Mats M H A gastric lesion produced by posterior pituitary extract Texas State
J Med 34 297 1938

- 359 Meulengracht E The medical treatment of peptic ulcer and its complications Brit
M J 2 301304 1900

- 360 Meyer, J. Markin M. and Necheles H. Studies on constitution and ulcer—III
Gastric secretion in the healthy members of ulcer families. *Am J Dig Dis & Nutr*
3: 474-486 1936

- 361 Milanes F. The pathological physiology of the stomach following subtotal gastrectomy for gastro duodenal ulcer. Am J Dig Dis & Nutr 3 186 188 1936

- 36° Miller G G Report on 230 cases of subtotal gastric resection for peptic ulcer. *BURGERY* 12: 383-39, 1940

- 363 Miller T G, and Karr W G Intubation studies of the human small intestine 111
The influence of variations in the reaction and the motility of the stomach contents
on the reaction and the motility of the intestinal contents Am J Roentg 35
300 303, 1936
- 364 Miyagawa Y The exact distribution of the gastric glands in man and in certain
animals J Anat 55 56 67, 19-0
- 365 Montgomery, A H Gastrojejunal ulcer—an experimental study Arch Surg 6
136 150, 1923
- 366 Moore F D Re section of the vagus nerves for ulcer—an interim evaluation—I
Operative technic and hospital management Arch Surg 55 164 170 1947
- 367 Moore F D Current practices in the surgical treatment of ulcer, S Clin. North
America 27 1071 1087 1947
- 368 Moore F D Chapman W P Schulz M D and Jones C M Transdiaphragmatic
re section of the vagus nerves for peptic ulcer New England J Med 234 241 251,
1946
- 369 Morrison S A modern conception of gastric secretory functions based upon recent
investigations and newer interpretations Am J Dig Dis 5 617 627 1939
- 370 Morton C B Observations on peptic ulcer—I A method of producing chronic
gastric ulcer Ann Surg 85 207 211 1927
- 371 Morton C B Observations on peptic ulcer—II A roentgenologic study of experi-
mental chronic ulcer Ann Surg 885 221 229 1927
- 372 Morton C B Observations on peptic ulcer—III Healing of experimental peptic ulcer
373 n in the
374 produced
2 19-8
375 ucal ex
376 experi
377 Morton C B Observations on peptic ulcer Experiments indicating the etiologic
importance of chemical and mechanical factors and their relationship to pyloric
dysfunction South Surgeon 3 316 325 1934
- 378 Morton C B and Graham J B Observations on peptic ulcer—VII Clinical contro-
loration of experimental data Ann Surg 91 74 1930
- 379 Movvihan B 26 1928
- 380 Murkin J R 13-4 1930
- 381 Necheles H L The fate of
organs impl
- 382 Neilson N M and Biever R F The reaction and physiology of the hepatic duct
and cytobile of various laboratory animals J Inf Dis 28 510 541 19-1
- 383 Newburger N Gastric operations for benign and malignant conditions, Ann Surg
106 200 20-0 1937
- 384 Ochner A Gage M and Hixon K Relationship of peptic ulceration to gastric
chemi Proc Soc Exp Biol & Med 31 126 126- 1934
- 385 Orlow W H The approach to gastric surgery Lancet 2 293 299 1938
- 386 Okala S On the reaction of bile J Physiol 50 114 118 1915
- 387 Olch I Y Duodenal regurgitation as a factor in neutralization of gastric acidity
Arch Surg 16 125 18 19-4
- 388 Oliver J V Effect of vagotomy on development of Mann-Williamson ulcer in the
dog Arch Surg 55 180 188 1947
- 389 Ophul W Gastric ulcers in rabbits following resection of the pneumogastric nerves
below the diaphragm J Exp Med 8 181 192 1906
- 390 Ornlorff J P Bergh G S and Ivy A C Peptic ulcer and the anxiety complex—
The failure of pharmacologically sustained hypersecretion and hyperactivity of the
stomach to produce chronic gastric ulcer in dog Surg Gyn. & Obst 61 162 166
19-5
- 391 Ornlorff J R Faules C P and Ivy A C The prophylactic value of gastric mucin
in the therapy of postoperative jejunal ulcer—an experimental study in dogs
Am J Dig Dis & Nutr 3 26 31 1936
- 392 O'Shaughnessy J L Physiology of peptic ulcer Lancet 220 177 181 1931
- 393 Owings J C and Smith J H Experimental production and care of jejunal ulcer
Proc Soc Exp Biol & Med 29 432 433 19-5
- 394 Owings J C and Smith I H The etiology of duodenal ulcer Proc Soc Exp
Biol & Med 29 833 835 1937
- 395 Palmer W L Peptic ulcer and gastric secretion Arch. Surg 44 452-472 1942

- 396 Palmer W L Medical management of peptic ulcer Symposium on gastroenterology
—Duke University, Oct 17 1947
397 Pavlov, I I The work of the digestive glands, Translated by W H Thompson J B

Reevaluation of the role of the pyloric antrum in
Coll Surgeons 32 236 1947

tic pepsin by histamine, J Clin Investigation 11

398 Price E B and Lee T F The gastric digestion of living tissue Surg Gyn, & Obst 83 617, 1946

- 403 Price E B Repair in the normal and hyperacid stomach—An experimental study,
Surg, Gyn & Obst 86 5167 1948
406 Price E B and Lee T F The gastric digestion of living tissue Surg Gyn, &
Obst 83 617, 1946
407 Price E B and Lee T F Digestion of living tissue by the hyperacid stomach—an
experimental study, Surg Gyn & Obst 84 859 911 1947
408 Priestley J T Some physiological aspects of the surgical treatment of duodenal ulcer
S Clin North America 27 906 918 1947
409 Priestley J T and Mann F C Gastric acidity with special reference to the para-
pyloric and pyloric mucosa—an experimental study Arch Surg 25 390 403 1937
410 Probasco J V Peptic ulcer S Clin North America 24 5059 1944
411 Rowell C B The discharge of bile into the duodenum—an experimental study
Arch Surg 23 1017 1021 1931

—the

on

surg

m

16

- 416 Priestley J T An analysis of the results of the surgical treatment of 216 con-
secutive cases of chronic peptic ulcer of the duodenum Ann Surg 121 583 591 1945
417 River A B Clinical consideration of the etiology of peptic ulcer Arch Int Med 83
641 649 1944

- 418 Robb The effect of caffeine upon gastric secretion in the dog,

419 Robb

420 Robb

421 Robb

422 Robb

- 423 Rosenow F C The causation of gastric and duodenal ulcer by stimulation
Dis 19 33, 34 1916

- 424 Roth J A and Ivy A C The pathogenesis of caffeine induced ulcers SURGERY 17
641 649 1945

- 425 Roth J A and Ivy A C The experimental production of acute and subacute ulcers
in cats by intramuscular injection of caffeine in bar wax Gastroenterology 2 274
1944

- 426 Roth J A and Ivy A C The effect of caffeine upon gastric secretion in the dog,

- 427 Roth peptic ulcer—Relation of
neuro, diagnosis and prognosis

- 428 Ross vagotomy in the treatment
of peptic ulcer

- 396 Palmer W L Medical management of peptic ulcer Symposium on gastroenterology
—Duke University Oct 17 1947
- 397 Palmer W L The role of the digestive glands Translated by W H Thompson, J B
ion of the role of the pyloric antrum in
glands 32 236, 1944
by histamine, J Clin Investigation 11
- 440-454 1932
The gastric value of determinations of pepsin
Surg 66 122, 1917
- ic secretions, Proc Soc Exper
- 404 Lortie S A and Portier B Effects of subtotal gastrectomy on gastric secretion
Experimental studies by use of a Laylor pouch in dogs, J A M A 86 836 879
1926
- 405 Price I B Pepsin in the normal and hyperacid stomach—An experimental study
Surg Gyn, & Obst 86 536, 1948
- 406 Price I B and Lee T F The gastric digestion of living tissue Surg, Gyn, &
Obst 87 1172 1946
- 407 Price
h—an
- 408 Price
ulcer
- 409 Price
e per
193
- 410 Price
study
- 411 Price
Arch Surg 23 1015 1021 1931
Note physiology of the stomach the pylorus and the duodenum with
h Surg 43 414 431, 1942
in ulcer—a study of end results Ann
the stomach and duodenum and their
438, 1926
in the gastric antrum and duodenum
al regulation Am J Surg 7 516
- 416 Riehoff W F An analysis of the results of the surgical treatment of 260 consecutive
cases of chronic peptic ulcer of the duodenum Ann Surg 121 593 599 1945
- 417 Rivers A B Clinical consideration of the etiology of peptic ulcer Arch Int Med 53
97 119 1944
- 418 Robert W M
the reality of
fats on
- 419 Robinon C S
Caffeine and peptic ulcer—Relation of
diagnosis and man
omy in the treatment
- 420 Knowlton E C The causation of gastric ulcers J Infect
Dis 19 384 1916
- 421 Roth J A and Ivy A C The pathogenesis of caffeine induced ulcers SURGERY 17
644 649 1943
- 422 Roth J A and Ivy A C The experimental production of acute and subacute ulcers
in cats by intramuscular injection of caffeine in bee wax Gastroenterology 2 24
28, 1944
- 423 Roth, J A and Ivy A C The effect of caffeine upon gastric secretion in the dog
cat and man Am J Physiol 141 454 461 1944

- 485 Vale C F Gastric resection for ulcer—experience in forty four cases Am J Surg 55 500 503, 1942
- 486 Van Wagoner, F H and Churchill, T P Production of gastric and duodenal ulcers in experimental cinchophen poisoning J A M A 99 1859 1860, 1932
- 487 Vanzant F R Late effects of section of the vagus nerves on gastric acidity Am J Physiol 99 345 378 1931
- 488 Vanzant F P, Alvarez, W C Eusterman G B, Dunn H L, and Berkson, J The normal range of gastric acidity from youth to old age—the analysis of 3,746 records Arch Int Med 49 340 359 1922
- 489 Vanzant F P, Alvarez, W C, and Rivers A B Studies of the influence of gastric and duodenal disease Am J Surg 61 100 104, 1941
- 490 Vane and Wangenstein O H Duodenal ulcer formation in the dog by intramuscular injections of a histamine beeswax mixture Am J Physiol 133 475 476 1941
- 491 Vineberg A M The activation of different elements of the gastric secretion by variation of vagal stimuli Am J Physiol 96 367 369, 1931
- 492 Vineberg A M and Babkin B P Histamine and pilocarpin in relation to the gastric secretion, Am J Physiol 97 69 73 1931
- 493 Vitkin S F Motor functions of the stomach after resection Ann Surg 111 2, 49, 1940
- 494 Walpole, H Varco R L Cole, C F, and Wangenstein O H Production of gastric and duodenal ulcers in the cat by intramuscular implantation of histamine, Proc Soc Exper Biol & Med 44 619 621 1940
- 495 Walter W The choice of surgical procedures for duodenal ulcer, Ann Surg 96 258 268 1932
- 496 Walters W Gastric acidity following operations for gastric and duodenal ulcer Its effect on the question of partial gastrectomy Ann Surg 104 585 593 1936
- 497 Walters W Should gastric resection be done for duodenal ulcer? Surgery 2 759 768 1937
- 498 Walters W Lewis E B and Lemon R G Primary partial gastrectomy (Polya type) for duodenal ulcer—a study of results in 212 cases Surg Gyn & Obst 71 240 243 1940
- 499 Walters W, Neill H A, Piller W E, Smith J T, and Varco R L Duodenal ulcer resection by a neurectomy in the treat
- 500 Walton A J
- 501 Walton A J Gastrojejunal ulceration Brit J Surg 22 33 55, 1934
- 502 Wangenstein O H The problem of surgical arrest of massive hemorrhage in duodenal ulcer SURGERY 8 275 1940
- 503 Wangenstein O H The surgeon and the ulcer problem Illinois M J 80 100 110 Aug 1941
- 504 Wangenstein O H Method of closing the pyloro antral pouch in the antral exclusion operation SURGERY 12 731 741, 1942
- 505 Wangenstein O H The surgical management of ulcer—A chemical problem Proc Internt Post grad M A N A 70 178 1942
- 506 Wangenstein O H Clinical aspects of the ulcer problem, Minnesota Med 27 714 1944
- 507 Wangenstein O H Causes of failure after gastric resection for ulcer Wisconsin M J 44 8 8 1945
- 508 Wangenstein O H The ulcer problem (Seventh Listerian Oration) Canad M A J 53 69 1945
- 509 Wangenstein O H Studies in etiology and surgical management of ulcer Symposium 1947
- 510 Wangenstein O H An acceptable operation for ulcer—
- 511 Wangenstein O H Hematemesis is from erosion or ulcer (Gastric and/or duodenal) An occasional complication of fracture Bull Am Coll Surg 30 58 1945
- 512 Wangenstein O H Varco P L Hay L J Walpole S W and Trach B H Gastric acidity before and after operative procedure with special reference to the role of the pylorus and antrum Ann. Surg 112 626 630 1940
- 513 Warren R Ulcer with report of an unsuccessful
- 514 Watson

study of the gastric and duodenal
1943

- 456 Small J T Denervation of the stomach, Arch Surg 55 189 201 1947
- 457 Smith, G M An experimental study of the relation of bile to ulceration of the mucous membrane of the stomach, J Med Research 30 147 184, 1914
- 458 Smith D T, and McConkey, M Peptic ulcer (gastric, pyloric and duodenal)—Occurrence in guinea pigs fed on a diet deficient in vitamin C, Arch Int Med 51 414 421, 1933
- 459 Somervell T H Physiological gastrectomy The operation of ligation of the arteries of the stomach to relieve hyperacidity and to prevent recurrent ulceration after gastroenterostomy, Brit J Surg 33 146 150 1945
- 460 Spencer, W H Meyer, G P, Ruffess M F and Hawk, P B Gastrointestinal studies VII Direct evidence of duodenal regurgitation and its influence upon the chemistry and function of the normal human stomach, Am J Physiol 39 459 479, 1915
- 461 Spencer, W H Meyer, G P, Ruffess M F and Hawk, P B Experimental studies on the production

- 462 Thomas J L Clinical studies on the role in gastric evacuation Am J Physiol 54 390 413 1917
- 463 Thornton L F, Storer L A, and L R Supradiaphragmatic section of the vagus nerves—Effect on gastric secretion and motility in patients with peptic ulcer J A M A 130 764 769, 1946
- 464 Thorpe J H The physiology of the peptic cells in man
- 465 Thorpe J H The physiology of the peptic cells in man
- 466 Thorpe J H The physiology of the peptic cells in man
- 467 Thorpe J H The physiology of the peptic cells in man
- 468 Thorpe J H The physiology of the peptic cells in man
- 469 Thorpe J H The physiology of the peptic cells in man
- 470 Thorpe J H The physiology of the peptic cells in man
- 471 Thorpe J H The physiology of the peptic cells in man
- 472 Truesdale P E The pylorus Observations upon its musculature Surg, Gyn & Obst 303 1915
- 473 Truesdale P E The pylorus Observations upon its musculature Surg, Gyn & Obst 303 1915
- 474 Truesdale P E The pylorus Observations upon its musculature Surg, Gyn & Obst 303 1915
- 475 Truesdale P E The pylorus Observations upon its musculature Surg, Gyn & Obst 303 1915
- 476 Truesdale P E The pylorus Observations upon its musculature Surg, Gyn & Obst 303 1915
- 477 Truesdale P E The pylorus Observations upon its musculature Surg, Gyn & Obst 303 1915
- 478 Truesdale P E The pylorus Observations upon its musculature Surg, Gyn & Obst 303 1915
- 479 Truesdale P E The pylorus Observations upon its musculature Surg, Gyn & Obst 303 1915
- 480 Truesdale P E The pylorus Observations upon its musculature Surg, Gyn & Obst 303 1915
- 481 Truesdale P E The pylorus Observations upon its musculature Surg, Gyn & Obst 303 1915
- 482 Truesdale P E The pylorus Observations upon its musculature Surg, Gyn & Obst 303 1915
- 483 Truesdale P E The pylorus Observations upon its musculature Surg, Gyn & Obst 303 1915
- 484 Truesdale P E The pylorus Observations upon its musculature Surg, Gyn & Obst 303 1915

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THE RATE OF CONVERSION OF ADMINISTERED INORGANIC RADIOACTIVE IODINE INTO PROTEIN BOUND IODINE OF PLASMA AS AN AID IN THE EVALUATION OF THYROID FUNCTION

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(From the Department of Surgery of the University of Chicago)

RADIOACTIVE iodine is being employed today by many investigators not only in the treatment of diseases of the thyroid but as a means of studying the function of the thyroid gland. Two methods—urinary excretion and uptake by the thyroid gland—have been used in following the fate of administered radioactive iodine in the various thyroid states. Extensive studies on the rate of excretion of radioactive iodine in cases of hyperthyroidism, euthyroidism, and hypothyroidism have been made by a number of investigators.¹⁻⁵ While this method has the advantage of simplicity, it requires the assumption that the iodine which is not excreted in the urine must be in the thyroid gland. Poor correlation was found by Quimby and McCune⁶ between values for thyroid uptake as determined by direct measurement over the gland and those computed from urinary excretion. Hamilton and Sole,⁷ Hertz, Roberts, and Salter¹ could not account for the total dose by combining the estimated content of the thyroid gland and the calculated amount excreted in the urine. Further disadvantages are in the wide range of excretion rate in the various thyroid states and the inaccuracy in urine collection. McArthur and associates⁸ found that the mean urinary excretion in thyrotoxic patients was 25 per cent, range 7 to 45 per cent, and in euthyroids the average was 59 per cent, range 23 to 98 per cent. In the range of 20 to 40 per cent there was a considerable overlapping between the thyrotoxic and nonthyrotoxic individuals. In hypothyroid subjects the range of elimination was from 75 to 95 per cent. The discovery of a low excretion is an adjunct in establishing the diagnosis of thyrotoxicosis.

This work was aided in part by the Charles H. and Mary F. S. Worcester Memorial Fund and by an institutional grant from the American Cancer Society.

Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 4-6, 1949.

The radioactive iodine used in this investigation was supplied by the Oak Ridge National Laboratories, Oak Ridge, Tenn., and obtained under allocation from the United States Atomic Energy Commission.

- 510 Watts S H A case of peptic ulcer in the jejunum of a dog following gastroenterostomy with a review of the cases reported in man, Johns Hopkins Hosp Bull 14 191 193 1903
- 516 Weech A A and Paige B H Nutritional edema in the dog IV Peptic ulcer produced by the same low protein diet that lends to hypoproteinemia and edema, Am J Path 13 49 50 1957
- 517 Weeks C Ryan B J, and VanIsyoy, J M Two deaths associated with supra diaphragmatic vagotomy J A M A 132 988 990 1910
- 518 Weir J F Phenomena including recurrent ulcer following resection of benign lesions Am J Surg 7 500 510 1954
- 519 Weiss A G, and Aron E Role des acides amines dans l'évolution de l'ulcère expérimental Influence de l'histidine La Presse Médicale 41 1880 1883 1955
- 520 Weiss A G Graves A and Curriaran G La dérivation intragastrique des sucres alcalins duodénaux C R Acad Sci Biol 109 916 920 1955
- 521 Weiss A G and Curriaran G Sur une méthode permettant d'obtenir des ulcères duodénaux par dérivation intragastrique des sucres alcalins C R Acad Sci Biol 109 920 925 1955
- 522 Wigglesworth J P The mechanism of the production of chronic duodenal ulcer Internat J Surg 1 1 1955
- 523 Wigglesworth J P The mechanism of the production of chronic duodenal ulcer Internat J Surg 1 1 1955
- 524 Wigglesworth J P The mechanism of the production of chronic duodenal ulcer Internat J Surg 1 1 1955
- 525 Wigglesworth J P The mechanism of the production of chronic duodenal ulcer Internat J Surg 1 1 1955
- 526 Wigglesworth J P The mechanism of the production of chronic duodenal ulcer Internat J Surg 1 1 1955
- 527 Wigglesworth J P The mechanism of the production of chronic duodenal ulcer Internat J Surg 1 1 1955
- 528 Wigglesworth J P The mechanism of the production of chronic duodenal ulcer Internat J Surg 1 1 1955
- 529 Wigglesworth J P The mechanism of the production of chronic duodenal ulcer Internat J Surg 1 1 1955
- 530 Wilkie D P D Jejunal ulcer—some observations on its complications and their treatment Ann Surg 40 1 107 1954

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The radioactive iodine used in this investigation was supplied by the Oak Ridge National Laboratories, Oak Ridge, Tenn., and obtained under allocation from the United States Atomic Energy Commission.

- 515 Watts S H A case of peptic ulcer in the jejunum of a dog following gastroenterostomy with a review of the cases reported in man, Johns Hopkins Hosp Bull 14 191 191, 1903
- 516 Weech A A and Page B H Nutritional edema in the dog IV Peptic ulcer produced by the same low protein diet that lends to hypoproteinemia and edema, Am J Path 13 49 206 19 7
- 517 Weeks C, Ryan B J, and VanHoy, J M Two deaths associated with supra-diaphragmatic vagotomy J A M A 132 985 990 1946
- 518 Weir J F Phenomena including recurrent ulcer following resection of benign lesion Am J Surg 7 300 515 19 1
- 519 Weiss A G and Aron F Role des acides amines dans l'évolution de l'ulcère expérimental Influence de l'histidine La Presse Médicale 41 1850 1883 1933
- 520 Weiss A G Graves A and Curran G La dérivation intragastrique des acides aminés permet-elle d'obtenir des ulcères expérimentaux? Biol. 102 48 50 19 9
- 521 Weiss A G and Curran G The effect of gastric diversion on the development of gastric ulcer Internat J Surg 1 1 1936
- 522 Weiss A G and Curran G The effect of gastric diversion on the development of gastric ulcer Internat J Surg 1 1 1936
- 523 Weiss A G and Curran G The effect of gastric diversion on the development of gastric ulcer Internat J Surg 1 1 1936
- 524 Weiss A G and Curran G The effect of gastric diversion on the development of gastric ulcer Internat J Surg 1 1 1936
- 525 Weiss A G and Curran G The effect of gastric diversion on the development of gastric ulcer Internat J Surg 1 1 1936
- 526 Weiss A G and Curran G The effect of gastric diversion on the development of gastric ulcer Internat J Surg 1 1 1936
- 527 Weiss A G and Curran G The effect of gastric diversion on the development of gastric ulcer Internat J Surg 1 1 1936
- 528 Weiss A G and Curran G The effect of gastric diversion on the development of gastric ulcer Internat J Surg 1 1 1936
- 529 Weiss A G and Curran G The effect of gastric diversion on the development of gastric ulcer Internat J Surg 1 1 1936
- 530 Wilkie D P D Jejunal ulcer—some observations on its complications and their treatment Ann Surg 99 401 409 1934
- 531 Wilkie D P D and Curran G The effect of gastric diversion on the development of gastric ulcer Internat J Surg 1 1 1936
- 532 Wilkie D P D and Curran G The effect of gastric diversion on the development of gastric ulcer Internat J Surg 1 1 1936
- 533 Wilkie D P D and Curran G The effect of gastric diversion on the development of gastric ulcer Internat J Surg 1 1 1936
- 534 Wilkie D P D and Curran G The effect of gastric diversion on the development of gastric ulcer Internat J Surg 1 1 1936
- 535 Wilkie D P D and Curran G The effect of gastric diversion on the development of gastric ulcer Internat J Surg 1 1 1936
- 536 Wilkie D P D and Curran G The effect of gastric diversion on the development of gastric ulcer Internat J Surg 1 1 1936
- 537 Wilkie D P D and Curran G The effect of gastric diversion on the development of gastric ulcer Internat J Surg 1 1 1936
- 538 Wilkie D P D and Curran G The effect of gastric diversion on the development of gastric ulcer Internat J Surg 1 1 1936
- 539 Wilkie D P D and Curran G The effect of gastric diversion on the development of gastric ulcer Internat J Surg 1 1 1936
- 540 Wilkie D P D and Curran G The effect of gastric diversion on the development of gastric ulcer Internat J Surg 1 1 1936
- 541 Zollinger R The surgical treatment of gastric and duodenal ulcer Surgery 1 4 1940

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THE RATE OF CONVERSION OF ADMINISTERED INORGANIC RADIOACTIVE IODINE INTO PROTEIN BOUND IODINE OF PLASMA AS AN AID IN THE EVALUATION OF THYROID FUNCTION

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RADIOACTIVE iodine is being employed today by many investigators, not only in the treatment of diseases of the thyroid but as a means of studying the function of the thyroid gland. Two methods—urinary excretion and uptake by the thyroid gland—have been used in following the fate of administered radioactive iodine in the various thyroid states. Extensive studies on the rate of excretion of radioactive iodine in cases of hyperthyroidism, euthyroidism, and hypothyroidism have been made by a number of investigators.¹⁻⁵ While this method has the advantage of simplicity, it requires the assumption that the iodine which is not excreted in the urine must be in the thyroid gland. Poor correlation was found by Quimby and McCune⁶ between values for thyroid uptake as determined by direct measurement over the gland and those computed from urinary excretion. Hamilton and Soley,⁴ Hertz, Roberts, and Salter¹ could not account for the total dose by combining the estimated content of the thyroid gland and the calculated amount excreted in the urine. Further disadvantages are in the wide range of excretion rate in the various thyroid states and the inaccuracy in urine collection. McArthur and associates⁵ found that the mean urinary excretion in thyrotoxic patients was 25 per cent, range 7 to 45 per cent, and in euthyroids the average was 59 per cent, range 23 to 98 per cent. In the range of 20 to 40 per cent there was a considerable overlapping between the thyrotoxic and nonthyrotoxic individuals. In hypothyroid subjects the range of elimination was from 75 to 95 per cent. The discovery of a low excretion is an adjunct in establishing the diagnosis of thyrotoxicosis,

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particularly in cases where the diagnosis is not clear. The finding of a high urinary excretion facilitates the exclusion of thyrotoxicosis in patients with hypermetabolism due to other diseases such as leucemia, lymphoma, hypertension and cardiac failure.

Measurement of the uptake permits a study of the rate and extent of the concentration of radioiodine in the gland. Werner, Quimby, and Schmidt⁸ have made a very careful study of the uptake in various thyroid conditions. They based their results on the per cent uptake of a tracer dose in twenty-four hours. The normal range of uptake was between 10 per cent and 30 to 40 per cent. An uptake in excess of 50 per cent was held to be specific for thyroid overactivity. There was a slight overlap of uptake between the euthyroid and hyperthyroid patients. Stanley and Astwood⁹ have used the rate of accumulation during a given period as an index of thyroid function. By plotting the number of counts per second against the square root of the time in minutes a straight line of uptake is revealed in the first four to six hours and the slope of this line is calculated. They have termed the slope of the line as the accumulation gradient. This method may narrow the percentage overlap between the normal and thyrotoxic patients but to date it has been applied only to the evaluation of the effectiveness of the antithyroid drugs.

The level of protein bound iodine in the plasma as determined chemically seems to be a good indicator of thyroid activity and correlates well with the basal metabolic rate and the clinical findings.¹¹⁻¹³ The methods are rather complicated, expensive and time consuming. Erroneous values due to contamination may occasionally occur.

Chaikoff, Turog, and Remhardt¹⁴ found that the rate of incorporation of injected radioactive iodine into the protein bound iodine fraction of plasma is depressed in thyroidectomized rats and increased in rats and guinea pigs injected with thyrotropic hormone and suggested that the rate of conversion may be a useful guide to thyroid activity.

The present investigation was undertaken to determine whether the rate of conversion of orally administered inorganic radioactive iodine into protein bound iodine of the plasma would be a useful guide clinically in determining thyroid activity, particularly in borderline cases of hyperthyroidism and hypothyroidism.

PROCEDURE

Radioactive inorganic iodine (I^{131}) containing no carrier was administered by mouth to patients with varying degrees of thyroid function. Patients who were thought to have a normal or a low thyroid activity received 0.5 to 1.5 millicuries.* Individuals who had an elevated basal metabolic rate and were clinically classical hyperthyroid patients were given either a large tracer dose or a therapeutic amount of radioactive iodine. This latter dose varied from 3 to 8 millicuries* depending upon the estimated size of the gland. None of the patients was fasted or on a special diet. Many of the cases were studied in the outpatient department.

Blood for determining the total amount of radioactive iodine in a given amount of plasma, and the per cent of this which was protein bound was drawn in exactly twenty four hours. The blood (15 cc) was placed in a tube containing 5 drops of heparin. The plasma was separated by centrifugation. The total plasma I^{131} was determined by pipetting 1 cc of plasma into a small porcelain capsule adding 1 cc of a diluting medium (0.2 M NaOH, 0.015 M KI, 0.05 M NaHSO₃) and 1 drop of silver nitrate solution (1 mg AgNO₃ per milliliter). The capsule was gently shaken and dried by means of an infrared lamp within a closed hood. Care was taken to insure that the dried residue was uniformly distributed over the bottom of the capsule. The radioactivity was determined by means of a Geiger Mueller counter. The method for determining the protein bound I^{131} was similar to that used by Chaikoff, Taurog and Reinhardt¹⁰. Plasma proteins were precipitated by adding 4 cc of 10 per cent trichloroacetic acid to 1 cc of plasma. The precipitate was separated by centrifugation and washed twice each time with 4 cc of 10 per cent trichloroacetic acid. The precipitate was dissolved with 7 drops of 2 N NaOH in 2 cc of distilled water and transferred to a porcelain capsule. The tube was washed twice with small amounts of distilled water. One drop of silver nitrate solution (1 mg AgNO₃ per milliliter) was added to the capsule. Radioactivity was determined after drying under an infrared lamp. Self absorption was found to be negligible when 1 cc of plasma and small amounts of sodium hydroxide were used.

The results were expressed as the ratio of radioactivity in counts per second in the protein fraction to the total plasma radioactivity in counts per second. We have designated this as the conversion ratio.

$$\text{Conversion ratio} = \frac{\text{Protein bound } I^{131} \text{ in c/s} \times 100}{\text{Total plasma } I^{131} \text{ in c/s}}$$

The conversion ratio was determined as soon as possible after the basal metabolism test had been obtained. Each of the cases received individual evaluation and was classified on the basis of the final clinical diagnosis. A careful history was obtained in reference to previous medication when medication was discontinued and if any recent laboratory procedure which involved the use of an iodized solution had been performed.

RESULTS

Patients With Hyperthyroidism—Twenty eight patients in whom the ultimate diagnosis was hyperthyroidism were included in this group (Table I) or presented a classical responding to therapy.

per cent (Fig. 1). Only one patient showed a turnover under 50 per cent. This patient (Case 1 S P) had discontinued propylthiouracil only two weeks prior to the test and had very minimal signs of recurrence. From subsequent experience if four weeks had been allowed to elapse before determining the conversion ratio this patient would have probably had a ratio above 50 per cent.

There seemed to be a relative correlation between the severity of the hyperthyroidism and the conversion ratio. Those cases where the rate of

particularly in cases where the diagnosis is not clear. The finding of a high urinary excretion facilitates the exclusion of thyrotoxicosis in patients with hypermetabolism due to other diseases such as leucemia, lymphoma, hypertension, and cardiac failure.

Measurement of the uptake permits a study of the rate and extent of the concentration of radioiodine in the gland. Werner, Quimby and Schmidt⁴ have made a very careful study of the uptake in various thyroid conditions. They based their results on the per cent uptake of a tracer dose in twenty-four hours. The normal range of uptake was between 10 per cent and 35 to 40 per cent. An uptake in excess of 50 per cent was held to be specific for thyroid overactivity. There was a slight overlap of uptake between the euthyroid and hyperthyroid patients. Stanley and Astwood⁹ have used the rate of accumulation during a given period as an index of thyroid function. By plotting the number of counts per second against the square root of the time in minutes a straight line of uptake is revealed in the first four to six hours and the slope of this line is calculated. They have termed the slope of the line as the accumulation gradient. This method may narrow the percentage overlap between the normal and thyrotoxic patients but to date it has been applied only to the evaluation of the effectiveness of the antithyroid drugs.

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*Oak Ridge standard.

incorporation fell between 50 and 70 per cent had only mild signs and symptoms of thyrotoxicosis while the more toxic cases converted over 70 per cent. Every patient that clinically presented a picture of marked thyroid activity had a ratio of 90 per cent or over.

There was no overlapping between the upper limit of normal and the hyperthyroid patients. At the present time all patients with a conversion ratio of 50 per cent or higher are considered as having hyperthyroidism.

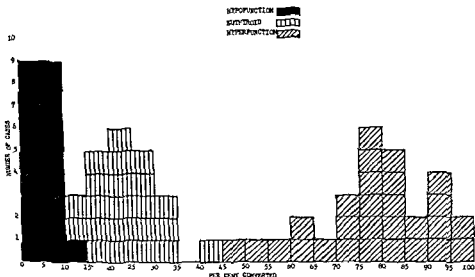


Fig 1—Distribution of conversion ratios in hyperthyroid, euthyroid and hypothyroid patients (Based on ultimate clinical diagnosis)

Case 16 (J R) is of particular interest and deserves special consideration. He was an elderly man who had been treated several years for heart disease. He exhibited very few signs of hyperthyroidism and the basal metabolic rate was +9. Radioiodine studies were done and the conversion ratio was 81 per cent. He was placed on propylthiouracil and the cardiac condition improved, he felt much better and gained twenty-two pounds of weight. When the propylthiouracil was discontinued he began to lose weight and the cardiac condition became worse. On the basis of this response this man was considered as being a masked hyperthyroid and was treated with radioactive iodine.

Patients With Euthyroidism—Twenty-two patients were studied who on the basis of clinical observation and the basal metabolic rate were thought to have an essentially normal thyroid activity (Table II). Sixteen of the group had diseases unrelated to the thyroid, three had benign adenomas, two had carcinomas of the thyroid which were treated by partial thyroidectomy and one had severe malignant exophthalmos. The latter (Case 15 M J) had repeated normal basal metabolic rates and showed no manifestations of hyperthyroidism. None of the numerous observers who saw this patient felt that she had thyrotoxicosis.

TABLE I CONVERSION RATIO IN HYPERTHYROIDISM

NO	PATIENT	AGE (YR.)	SEX	TYPE OF GLAND DISEASE	BMR	CONVERSION RATIO (IN %)	REMARKS
1	GI	50	M	Dif	+17	45	Off propylthiouracil for 2 weeks prior to I ¹³¹ therapy, previous thyroidectomy, diabetes, responded to I ¹³¹ treatment
2	ER	59	F	Dif	+21	53	Taking propylthiouracil 50 mg every other day, discontinued 1 week before I ¹³¹ therapy, previous thyroidectomy, responded to I ¹³¹ treatment
3	MK	59	F	Dif	+25	59	Osteoporosis, previous thyroidectomy, responded to I ¹³¹ treatment
4	HW	33	F	Nod	+22	61	Two previous thyroidectomies off propylthiouracil for 6 weeks responded to I ¹³¹ treatment
5	JR	25	M	Dif	+19	65	Off propylthiouracil for 4 weeks responded to I ¹³¹ therapy
6	VS	26	F	Dif	+39	68	Responded to propylthiouracil
7	BS	42	F	Nod	+42	71	Two previous thyroidectomies, no recent antithyroid drugs, responded to I ¹³¹ treatment
8	SB	30	M	Dif	+35	74	No previous medication, responded to I ¹³¹
9	AS	50	F	Dif	+42	75	No previous medication, responded to propylthiouracil
10	ED	40	F	Dif	+40	76	Off propylthiouracil for 2 months, responded to I ¹³¹ treatment
11	MI	53	F	Dif	+15	77	Off propylthiouracil for 6 weeks, responded to I ¹³¹ therapy
12	RE	76	M	Nod	+40	78	Parkinsonism, responded to propylthiouracil
13	EF	59	F	Nod	+36	78.9	Discontinued propylthiouracil for 1 month, responding to I ¹³¹ treatment
14	NM	32	F	Dif	+39	79	Responded to propylthiouracil
15	RH	37	F	Dif	+42	80	Stopped propylthiouracil for 3 weeks, responded to I ¹³¹ classical hyperthyroid
16	JR	70	M	Dif	+8	81	Responded to propylthiouracil, subsequently treated with I ¹³¹ cardiac
17	SW	52	F	Dif	+39	81	No previous medication, cardiac, treated with I ¹³¹ classical hyperthyroid
18	IF	29	F	Dif	+30	82	Off iodine therapy for 1 week, treated with propylthiouracil and thyroidectomy
19	AT	47	M	Dif	+32	80	Lugols for 3 days before I ¹³¹ therapy, classical thyrotoxicosis
20	IM	56	F	Dif	+43	80	Hypertension, stopped propylthiouracil for 3 weeks, responded to I ¹³¹ therapy
21	AD	62	F	Nod	+31	87.5	Stopped Lugols solution 2 weeks before, responded to I ¹³¹ therapy
22	FS	44	M	Dif	+59	90	No previous medication, responded to I ¹³¹ therapy
23	MB	60	F	Nod	+49	91.5	No previous medication, treated with I ¹³¹ classical thyrotoxicosis
24	TM	51	F	Dif	+28	91.8	No previous medication, responded to I ¹³¹ therapy
25	JH	31	F	Dif	+32	90	No previous medication, treated with propylthiouracil and thyroidectomy
26	MK	65	F	Dif	+30	90	Responded to I ¹³¹ treatment
27	FS	45	F	Nod	+64	90	Previous thyroidectomy, classical hyperthyroid, responded to I ¹³¹ treatment
28	RC	30	F	Dif	+42	96	Off antithyroid drugs for 1 month, treated with I ¹³¹ classical hyperthyroid

incorporation fell between 50 and 70 per cent had only mild signs and symptoms of thyrotoxicosis while the more toxic cases converted over 70 per cent. Every patient that clinically presented a picture of marked thyroid activity had a ratio of 90 per cent or over.

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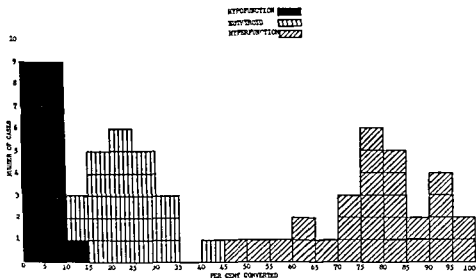


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TABLE I CONVERSION RATIO IN HYPERTHYROIDISM

NO	PATIENT	AGE (YR.)	SEX	TYPE OF CLAND	RR	CONVERSION RATIO (IN %)	REMARKS
1	SI	50	M	Dif	+11	40	Off propylthiouracil for 4 weeks prior to I ¹³¹ therapy, previous thyroidectomy, diabetes, responded to I ¹³¹ treatment
2	ER	58	F	Dif	+21	53	Taking propylthiouracil 50 mg every other day, discontinued 1 week before I ¹³¹ therapy, previous thyroidectomy, responded to I ¹³¹ treatment
3	MK	48	F	Dif	+20	59	Osteoporosis previous thyroidectomy, responded to I ¹³¹ treatment
4	HW	33	F	Nod	+23	61	Two previous thyroidectomies off propylthiouracil for 6 weeks responded to I ¹³¹ treatment
5	JR	20	M	Dif	+19	60	Off propylthiouracil for 4 weeks, responded to I ¹³¹ therapy
6	VS	26	F	Dif	+79	68	Responded to propylthiouracil
7	BS	40	F	Nod	+40	71	Two previous thyroidectomies no recent antithyroid drugs, responded to I ¹³¹ treatment
8	SB	35	M	Dif	+35	74	No previous medication responded to I ¹³¹
9	AS	52	F	Dif	+42	70	No previous medication, responded to propylthiouracil
10	FD	45	F	Dif	+45	76	Off propylthiouracil for 2 months responded to I ¹³¹ treatment
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18	IF	28	F	Dif	+0	80	Off iodine therapy for 1 week treated with propylthiouracil and thyroidectomy
19	AT	47	M	Dif	+32	80	Lugols for 3 days before I ¹³¹ therapy, classical thyrotoxicosis
20	IM	56	F	Dif	+43	80	Hypertension, stopped propylthiouracil for 3 weeks responded to I ¹³¹ therapy
21	AD	62	F	Nod	+31	87.5	Stopped Lugols solution 2 weeks before, responded to I ¹³¹ therapy
22	FS	44	M	Dif	+59	90	No previous medication, responded to I ¹³¹ therapy
23	MB	69	F	Nod	+49	91.5	No previous medication treated with I ¹³¹ classical thyrotoxicosis
24	TM	51	F	Dif	+28	91.8	No previous medication, responded to I ¹³¹ therapy
25	JH	31	F	Dif	+32	90	No previous medication treated with propylthiouracil and thyroidectomy
26	MK	65	F	Dif	+30	90	Responded to I ¹³¹ treatment
27	FS	45	F	Nod	+64	96	Previous thyroidectomy classical hyperthyroid responding to I ¹³¹ treatment
28	RC	30	F	Dif	+72	96	Off antithyroid drugs for 1 month treated with I ¹³¹ classical hyperthyroid

TABLE III CONVERSION RATIO IN HYPOTHYROIDISM

NO	PATIENT	AGE (YR)	SEX	DIAGNOSIS	B.M.R.	CONVERSION RATIO (IN %)
1	RB	20	M	Thyroid carcinoma total thyroidectomy myxedema	-20	30
2	FB	67	F	Myxedema	-40	50
3	FL	24	M	Carcinoma of thyroid, myxedema	-40	50
4	KD*	61	F	Carcinoma of thyroid	-6	27
5	MO	54	F	Carcinoma of thyroid myxedema	-75	125
6	RP*	11	M	Carcinoma of thyroid	-13	70
7	CS*	52	M	Carcinoma of thyroid myxedema	-13	4
8	PS	62	M	Hurthle cell carcinoma myxedema	-38	61
9	LS*	44	F	Carcinoma of thyroid	-4	50
10	MN	52	F	Carcinoma of thyroid	-0	71
11	AS	55	F	Myxema	-70	70
12	JK	41	F	Hypothyroidism pernicious anemia	-1	70
13	MB	9	F	Myxema	-2	70
14	JC*	9	M	Congenital hypothyroidism	-9	68
15	CO	44	M	Myxema	-37	7
16	MT	51	F	Post thyroidectomy hypothyroidism	-30	33
17	FW	17	M	Cranio-pharyngioma	-59	98
18	EH	44	F	Hypothyroidism anxiety state	-19	4
19	OI	53	M	Myxema mill	-18	9

Patient receiving thyroid extract

TABLE IV CONVERSION RATIO IN CARDIAC AND HYPERTENSIVE STATES

NO	NAME	AGE (YR)	SEX	DIAGNOSIS	B.M.R.	CONVERSION RATIO (IN %)
1	LS	61	F	Auricular fibrillation with myocardial defect diabetes mellitus	+3	7
2	AB	55	M	Hypertensive cardiovascular disease mild decompensation	+14	62
3	AG	67	F	Hypertensive cardiovascular disease with insufficiency nodular goiter	+36	15
4	TC	50	M	Mild cardiac failure	+11	5
5	EK	58	M	Hypertensive cardiovascular disease diabetes mellitus	+4	84
6	IM	71	F	Hypertensive cardiovascular disease	+25	8
7	CH	51	F	Hypertensive cardiovascular disease with moderate decompensation	+31	64
8	RI	9	M	Essential hypertension had sympathectomy	+31	36
9	EC	57	M	Essential hypertension no apparent cardiac disease	+22	238

Not included in Fig. 1

DISCUSSION

The chemical nature of protein bound iodine is not yet fully understood but it is generally accepted that its level in the plasma is a good index of circulating thyroid hormone. Bassett Coons, and Salter¹¹ found that about 30 per cent of the protein bound iodine is in a diiodotyrosine like fraction while the remainder is comprised of a thyroxine like fraction. In myxedema the thyroxine fraction practically disappears. In patients with normal or hyperactive thyroid function the increase in the protein bound iodine is due chiefly to the thyroxine like moiety. Morton Perlman and Chaikoff¹ administered tracer doses of radioiodine to normal guinea pigs and those treated for four days with thyrotropic hormone and studied the rate of incorporation of the labeled iodine into radioiodotyrosine and radiothyroxine at two and twenty six hours. By this method they showed that not only is the increase in the protein bound iodine in the hyperactive group due mainly to thyroxine, but the rate of its elaboration is considerably increased over the control group.

TABLE II CONVERSION RATIO IN EUTHYROIDISM

NO	NAME	AGE (YR)	SEX	DIAGNOSIS	BMR	CONVERSION RATIO (IN %)
1						
2						
3						
4						
5	BO	41	F	denal ulcer		
6	BC	30	F	Hemorrhoids anxiety symptoms	+10	94
7	FL	33	F	Carcinoma of thyroid subtotal thyroidec	+10	166
8	GR	7	F	tomy		
9	LA	29	F	Uterine fibroids transection of cord at L 2	-	70
10	FS	23	M	Carcinoma of thyroid	-10	21
11	MS	37	F	Intestinal obstruction	-	282
12	ML	74	F	Gastric ulcer	- 1	4
13	FD	39	F	Carcinoma of pancreas	-	337
14	CF	20	F	Biliary fistula	-14	71
15	MT	30	F	Carcinoma of breast previous subtotal thyroidectomy	-16	108
16	GS	26	M	Ulcerative colitis	+12	10
17	MT	30	F	Malignant exophthalmos no signs of thyrotoxicosis	- 1	4
18	AT	9	F	No organic disease	-23	6
19	FT	51	F	Adenoma of thyroid	- 2	17
20	IV	59	M	Functional bowel distress	+1	17
21	FT	27	F	Cyst of kidney	+ 3	18.5
22	FT	61	F	Inguinal hernia	-	70
23	FT	27	F	Appendicitis	-13	13
24	FB	61	F	Adenoma of thyroid	-11	133

The range of the conversion ratio was 13 to 42 per cent with an average of 24 per cent (Fig 1)

Patients With Hypothyroidism—The expected low conversion ratio in hypothyroidism or myxedema was confirmed in 19 cases (Table III). The range was from 27 to 125 per cent, with an average of 6 per cent. All of the cases in this group except one converted less than 10 per cent (Fig 1). Five of the patients were receiving thyroid extract which maintained their basal metabolic rate at a normal level. We have considered all patients who convert less than 10 per cent to have an abnormally low thyroid activity.

Werner Quimby and Schmidt⁴ found a very low uptake of radioiodine in six cases of acute thyroiditis despite a normal basal metabolic rate. In the one case which we studied these findings were confirmed. The patient had a basal metabolic rate of +6, low uptake over the thyroid converted only 64 per cent and excreted 85 per cent in seventy-two hours.

Patients With Cardiac Disease and Hypertension—Seven patients who had hypertensive cardiovascular disease with an elevated basal metabolic rate and two with essential hypertension without apparent cardiac disease but an elevated basal metabolic rate were studied (Table IV). In all the cases where there was marked cardiovascular disease the conversion ratio was under 10 per cent placing them in the hypothyroid range. This would suggest that the body has suppressed the action of the thyroid in order to decrease the metabolic activity and thus reduce the work of the heart. The essential hypertensive patients converted 36 and 218 per cent which would place them in the euthyroid group.

TABLE III CONVERSION RATIO IN HYPOTHYROIDISM

myxedema						
2	EB	67	F	Myxedema	-40	50
3	FL	44	M	Carcinoma of thyroid myxedema	-40	50
4	KD	65	F	Carcinoma of thyroid	-6	27
5	MO	54	F	Carcinoma of thyroid myxedema	-35	125
6	RP	11	M	Carcinoma of thyroid	-13	70
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17	FW	1	M	Craniohypopharyngioma	-39	88
18	FH	44	F	Hypothyroidism anxiety state	-19	4
19	OP	59	M	Myxedema mild	-18	9

* Patient receiving thyroid extract

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NO	NAME	AGE (YR.)	SEX	DIAGNOSIS	B M F	CONVERSION RATIO (IN %)
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6	IM	73	F	Hypertensive cardiovascular disease	+5	8
7	CH	51	F	Hypertensive cardiovascular disease with moderate decompression	+31	64
8	RI	1	M	Essential hypertension had sympathectomy	+31	36
9	EC	51	M	Essential hypertension no apparent cardiac disease	+2	238

Not included in Fig. 1

DISCUSSION

The chemical nature of protein bound iodine is not yet fully understood, but it is generally accepted that its level in the plasma is a good index of circulating thyroid hormone. Bassett, Coons and Salter¹¹ found that about 30 per cent of the protein bound iodine is in a diiodotyrosine like fraction while the remainder is comprised of a thyroxine like fraction. In myxedema the thyroxine fraction practically disappears. In patients with normal or hyperactive thyroid function the increase in the protein bound iodine is due chiefly to the thyroxine like moiety. Motton, Perlman and Chaikoff¹² administered tracer doses of radioiodine to normal guinea pigs and those treated for four days with thyrotropic hormone and studied the rate of incorporation of the labeled iodine into radioiodotyrosine and radiothyroxine at two and twenty six hours. By this method they showed that not only is the increase in the protein bound iodine in the hyperactive group due mainly to thyroxine but the rate of its elaboration is considerably increased over the control group.

No attempt was made in this study to fractionate the protein bound iodine in the various thyroid states but the greater conversion ratios in the euthyroid and hyperthyroid groups are presumably due to the increased production and elaboration of thyroglobulin. The data suggest that the rate of incorporation of radioiodine into newly formed protein bound iodine can be determined with sufficient accuracy to be of value in determining thyroid activity.

In such studies the possibility of an "exchange" reaction occurring as a purely physicochemical phenomena presents itself. If such a reaction occurred in this study, we believe it is negligible or the amount of radioiodine in the protein precipitate would be higher in patients with hypothyroidism, particularly those receiving thyroid extract. By *in vitro* tests of adding radioiodine to plasma we were unable to detect any appreciable iodination of protein.

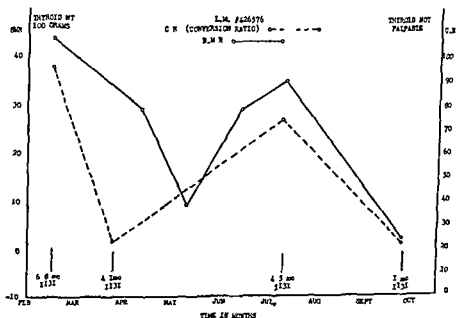


Fig. 2—Correlation between changes in conversion ratio and basal metabolic rate in a case of hyperthyroidism treated with radioactive iodine.

The change in the conversion ratio in relation to the basal metabolic rate in a case of true hyperthyroidism seems to be similar to that found by the

the conversion ratio and the treated with I¹³¹. Five weeks of the gland was changed so that the conversion ratio was normal but the basal metabolic rate was still quite high. Six weeks later the basal metabolic rate had fallen to almost normal. The amount of radioactive iodine given was not sufficient to effect a cure and the patient had a recurrence of the symptoms. The basal metabolic rate increased as did the conversion ratio. At the

time of the administration of the third dose of radioactive iodine the basal metabolic rate was lower than at the beginning of the treatment and the clinical manifestations were less severe. The conversion ratio was lower and correlated well with the other findings. The final dose of labeled iodine was given when the basal metabolic rate had again returned to normal, at which time the ratio was found to be in the euthyroid range.

There are many extra thyroidal factors which may influence the conversion ratio so that it is important to evaluate each case individually. Except in a few instances we have allowed a period of four weeks to elapse from the time of discontinuing antithyroid drugs thioevanate or cough syrups containing iodine before determining the conversion ratio. Recent cholecystograms, bronchograms, or pyelograms may also alter the rate of incorporation of tagged iodine into the protein bound fraction.

The type of gland did not seem to make any appreciable difference in the conversion ratio although most of the cases in the hyperthyroid group were thought to have diffusely hyperplastic glands. In the patients studied age did not seem to affect the conversion ratio. In many of the cases presented the urinary excretion and the uptake by the thyroid gland were determined. There was a good correlation in most of the cases between the conversion ratio, uptake, and excretion.

Doses of 1 to 15 millicuries were used in order to obtain significant counts in 1 cc of plasma. Although these are larger tracer doses than generally used, no adverse reactions have been observed. In cases of hyperthyroidism most all of them will require more I^{131} before a therapeutic response is obtained. In euthyroids approximately 50 per cent of the dose is excreted and the amount taken up by the gland is much less than that required to cause hypothyroidism. Crile, McCullagh, and Glasser¹² have estimated that it requires 30 millicuries to cause hypothyroidism in a patient with a normally functioning gland. Since it is well known from radioautograph methods that the localization of I^{131} in the thyroid gland is not uniform, the chances of having a small area intensely radiated are probably as great if 100 microcuries or 500 microcuries are fixed in the gland. The possibility of carcinoma developing in such an area warrants consideration, but there is no evidence either clinically or experimentally to suggest that the incidence will be significantly altered.

Many more cases with various thyroid states are being studied. Although in the cases presented there was no overlapping between the euthyroid and hyperthyroid group, it is possible that some overlapping may be found as more cases are studied since this procedure only estimates the rate of elaboration of the thyroid hormone and does not measure the sensitivity of the tissues to thyroxine.

SUMMARY AND CONCLUSIONS

- 1 The rate of conversion of orally administered radioactive iodine into the protein bound iodine of the plasma has been studied in patients with various thyroid states and in patients with hypertension and cardiac disease with an elevated basal metabolic rate.

- 2 In normal man the conversion ratio ranged from 13 to 42 per cent
- 3 All patients in whom the conversion ratio is 50 per cent or greater are considered to have a hyperactivity of the thyroid gland
- 4 There is no overlapping between the hyperthyroid group and the euthyroid group in the cases studied
- 5 Patients who convert 10 per cent or less are considered to have hypothyroid activity
- 6 All of the patients with severe cardiac disease but an elevated basal metabolic rate show a low conversion ratio
- 7 Two patients with hypertension but no apparent cardiac disease have a conversion ratio in the normal range
- 8 The results suggest that the rate of incorporation of radioactive iodine into protein bound iodine of the plasma may be a useful guide to thyroid activity

REFERENCES

- 1 Hertz S, Robert A and Salter W T Radioactive Iodine as an Indicator in Thyroid Physiology IV The Metabolism of Iodine in Graves Disease J Clin Investigation 21 191
- 2 Keating F R Jr Power M H Berkson J and Haines S F The Urinary Excretion of Radioiodine in Various Thyroid States J Clin Investigation 26 1138 1947
- 3 Skanck B N Radioactive Iodine Its Use in Studying the Urinary Excretion of Iodine in Humans in Various States of Thyroid Function Acta Med Scandinav (Quoted by Rawson and Skanck Radiology 51 50 1948)
- 4 Hamilton J G and Selvy M H Studies in Iodine Metabolism by the Use of a New Radioactive Isotope of Iodine Am J Physiol 127 107, 109
- 5 McArthur J W Rawson I W Ficharty R G and Means J H The Urinary Excretion of Radioactive Iodine as an Aid in the Diagnosis of Hyperthyroidism Ann Int Med 29 229 1948
- 6 Quimby F H and McCune D H Uptake of Radioactive Iodine by the Normal and Disordered Thyroid Gland in Children Radiology 19 201 1947
- 7 Warner S C Quimby F H and Schmidt C Clinical Experiences in Diagnosis and Treatment of Thyroid Disorders With Radioactive Iodine (Eight Day Half Life) Radiology 51 561 1948
- 8 Radioactive Iodine Test in the Treatment of the Thyroid Function in Man Brookhaven Symposium of the Relative Activities of Antithyroid Compounds in Man Using Radioactive Iodine Endocrinology 41 66 1947
- 9 Charkoff I J Tauger A and Reinhardt W O The Metabolic Significance of Protein Bound Iodine of Plasma A Study of Its Concentration Under Various Conditions and Its Rate of Formation as Measured With Radioactive Iodine Endocrinology 40 47 1947
- 10 Bassett A M Coons A H and Salter W T Protein Bound Iodine in Blood A Naturally Occurring Iodine Fraction and Their Chemical Behavior Am J M Sc 202 516 1941
- 11 Morton M E Perlman I and Charkoff I L Radioactive Iodine as an Indicator of the Effect of Thyrotropic Hormone on the Thyroid Gland and Plasma J Biol Radioactive Iodine in the Treatment of the Protein Bound Blood Iodine 1 1949
- 12 Curti Use of the Protein Bound Blood Iodine 128 443 1948
- 13 Protein Bound Iodine in Blood 8
- 14 Salter W T Bassett A M and Charkoff I L Its Relation to Thyroid Function in 100 Clinical Cases Am. J. M. Sc 202 527, 1941

POTASSIUM DEFICIENCY IN SURGICAL PATIENTS

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THE work of which this paper is a partial report began as an intensive study of fluid and electrolyte problems on the Surgical Service of the Presbyterian Hospital in June 1947 at which time the completion of a flame photometer made possible rapid and reasonably numerous determinations of sodium and potassium concentrations in biologic media. The opening of the surgical metabolic unit in January 1948 made possible the accurate balance study of fluid, electrolyte, and nitrogen exchanges in patients both pre- and postoperatively. Two parallel and dependent lines of study then evolved: the methodical study of patients in the metabolic unit according to plan and the day to day evaluation of the electrolyte and fluid status of critically ill patients on the general ward service with special effort being made to evaluate and correct electrolyte imbalance as found and to maintain major surgical cases in as close balance as possible postoperatively. This paper reports some of our experiences with particular emphasis on potassium deficiencies in surgical patients, their correction and prevention.

REVIEW OF PERTINENT LITERATURE

Since potassium is the major cation in the body, exceeding sodium by a ratio of more than two to one, the role of this ion in physiology has been the subject of numerous studies over a period of many years. Benedict¹ in 1915 showed that in starvation potassium was lost in direct relation to loss of nitrogen with 2.87 mM of K being lost with each gram of nitrogen in days 2 to 11 inclusive. Similar results were obtained by Gamble in 1923 with K loss slightly in excess of expectation based on nitrogen loss and tissue analysis. In 1933 Butler² reported large losses of potassium in the stools and urine of two infants with diarrhea and noted that the potassium loss far exceeded that expected from nitrogen loss. Darrow³ and Gamble⁴ in reporting metabolic studies on children with congenital alkalosis and diarrhea noted in addition to an excessive chloride loss in the stool which was considered to be the most significant factor in electrolyte imbalance, a very large loss of potassium in stool and in urine particularly during phases of increasing dehydration. Darrow observed plasma K levels as low as 1.5 meq. per liter in the untreated state and showed a decrease

in plasma potassium during dehydration with continuing potas-

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sum loss in urine and stools. He also demonstrated that a relative potassium deficit could appear during a period of markedly positive nitrogen balance and that potassium deficits were increased in periods of positive sodium balance. Although no symptoms other than generalized weakness were shown with the dehydration and K loss, the administration of additional potassium as KCl by mouth to supplement that taken in food proved of distinct benefit to the child.

In a paper discussing retention of electrolyte following acute diarrhea with severe dehydration in infants, Darrow⁶ demonstrated by metabolic studies that loss of K from cells may amount to as much as one quarter of the total body stores of K. Much of the extracellular dehydration in some cases appeared to be due to loss of sodium by shift of sodium and water into cells. The usual replacement of extracellular fluid with saline or saline bicarbonate mixtures restored extracellular deficits but actually increased potassium loss since additional sodium entered the cells. Two of his patients were treated with parenteral KCl and showed retention of K, Na and Cl with rapid improvement which was subsequently maintained with KCl by mouth. Goss and Darrow⁷ then reported a series of patients treated for infantile diarrhea and dehydration with a mixture of sodium and potassium chlorides and sodium lactate in which the mortality was only 3 of 50 as contrasted to 17 of 50 treated with sodium chloride and sodium lactate alone.

In diabetic acidosis Atchley and associates⁸ showed loss of intra- and extracellular electrolytes after insulin withdrawal and retention of these ions during the recovery period. In acidosis the K loss averaged 90 meq a day with nitrogen loss of 6.2 Gm. Danowski⁹ also demonstrated increased K loss and nitrogen loss in diabetic acidosis and noted that the serum K fell markedly in the recovery phase. Butler¹⁰ in recent metabolic studies of diabetic coma confirmed large potassium losses and used solutions containing potassium in repleta to avoid sharp reductions in plasma K concentrations.

A series of reports¹¹⁻¹³ of cases of potassium deficiency in the recovery period following diabetic acidosis have shown K levels of 1.9 to 2.5 meq per liter in plasma accompanied by muscular weakness, difficulties in swallowing and interference with respiration in one instance requiring a respirator but with rapid recovery following parenteral and oral administration of potassium salts.

Dehydration was studied extensively by Ilkinton and Winkler¹⁴ and their associates. They showed in the dog that in severe water depletion large amounts of potassium are excreted in high concentration by the kidneys. Great resistance to plasma K changes were noted and it was observed with dehydration in animals with ureters tied that there is no mobilization of intracellular potassium. They suggested that high plasma K levels seen in hemorrhage and intestinal obstruction are due to marked alteration in cell metabolism. In an earlier paper⁵ it was observed that 20 to 38 per cent of extracellular water could be lost while from 70 to 90 per cent of intracellular water was mobilized and that K loss was much greater than could be explained simply by tissue catabolism. In late stages sodium and chloride and

the extracellular fluid tended to be maintained while potassium and intracellular water losses rose steadily until K excretion in the urine reached 500 meq per liter. In human subjects early stages of the same phenomenon were observed. In the first forty eight hours of water deprivation extracellular losses predominated but later losses were predominantly intracellular, and again the potassium loss far exceeded that expected from catabolism alone. By the end of four days water deficits were proportional to the ratio of extracellular to intracellular water.¹⁶

Black, McCinere, and Young¹⁷ in a similar experiment with volunteers who ate a dry diet showed that extracellular sodium concentration rose while large amounts of potassium were excreted in urine. They stated that the kidney will preferentially excrete potassium over sodium or urea under these circumstances. Winkler and associates¹⁸ demonstrated that with water deprivation the ingestion of foods containing nitrogen or potassium increases the obligatory urine output and the rate of dehydration. Recent studies by Elkinton¹⁹ showed that potassium losses are great in dehydration and when extracellular sodium is high as when water loss is disproportionately greater than electrolyte loss. Cell sodium tends to be high under these conditions, while it is low in oliguria and in nephrectomized animals. The cell potassium is not necessarily elevated when cell sodium is low but is always low when cell sodium is high. Cell potassium rises only when an exogenous source of potassium is available.

Brown, Currens and Marchand⁶ reported potassium deficiency in three cases of nephritis with plasma levels of 20, 21, and 25 meq per liter and marked muscular weakness followed by rapid recovery on the administration of potassium salts. They described electrocardiographic changes characterized by depressed ST segments in all leads and low voltage T waves which returned to normal after potassium administration. Similar electrocardiographic changes were reported by Holler¹¹, in this connection it is of interest that Darrow and Miller¹ observed necrosis of myocardial fibers and replacement with fibroblasts in rats with potassium deficiency induced by desoxycorticosterone treatment.

Plasma potassium deficits have been observed at the time of crises of familial periodic paralysis by Ferrebee, Gerity, Atchley and Loeb² who also observed a decrease in renal excretion during attacks. Plasma K rose and renal excretion increased on recovery. In Cushing's syndrome Willson, Power and Kepler³ have reported plasma K values of 2.2 meq per liter together with a high HCO_3 and low Cl. This alkalosis was unresponsive to the administration of NH_4Cl but responded to the administration of either KCl or potassium citrate with retention of potassium drop in HCO_3 and rise in chloride.

Alkalosis has been reported as being associated with potassium deficiency states and perhaps causing them. Yannet and Darrow²⁴ reported wide variations in muscle K in relation to phosphate and nitrogen and observed that muscle water varied directly with cell sodium and potassium and inversely with the concentration of extracellular electrolytes. Yannet²⁵ in an acute

experiment in rats noted a rise in cell sodium with intraperitoneal bicarbonate administration. Darrow²⁶ found in rats with pyloric obstruction which were given glucose and water that serum K rose while serum Na and Cl fell as did cell sodium and chloride. On the other hand animals on diets low in chloride, and low in sodium potassium, and chloride, showed a rise in serum bicarbonate and fall in serum chloride accompanied by a rise in cell sodium and a fall in cell potassium. Serum potassiums were low in these animals. It was also noted that cell water tended to be increased as sodium replaced potassium milliequivalent for milliequivalent.

Darrow, Schwartz, Immucci, and Coville²⁷ have shown that there appears to be a definite and predictable relationship between serum bicarbonate and cell potassium once renal adjustment has been reached. In alkalosis produced in rats by a variety of means including low K intake and adrenal cortical hormone treatment, it was noted that the higher the serum bicarbonate the lower the cell potassium and the higher the cell sodium. It was concluded that patients having a potassium deficit may be expected to develop an alkalosis when treated only with sodium chloride and this alkalosis will be refractory to sodium chloride therapy if the potassium deficit persists. The experimental results to be reported in the present paper confirm these observations. Marked potassium deficit has been reported with adrenal cortical hormone administration by Kuhlmann, Ragan, Ferrebee, Atchley, and Loeb²⁸ and by Lacrebee, Parker, Carnes, Gerity, Atchley, and Loeb.²⁹ The first study reported plasma potassium values one half of normal with the development of marked muscular weakness which was cured by KCl administration and the second noted the replacement of muscle potassium by sodium in animals under treatment.

Intravenous fluids have been studied for their effect on electrolyte and water balance. Hastings and Fitchelberger³⁰ noted little change in intracellular volume with infusions of physiologic levels of sodium chloride and bicarbonate but an increase in intracellular volume when alkaline solutions were infused. Flock, Lohman, Minn, and Kendall³¹ showed that glucose infusions resulted in drops of plasma K levels in dogs as did infusions containing sodium ion particularly when combined with lactate or bicarbonate anions. The work of Fenn³² and others has suggested that potassium is involved in glycogen synthesis in the liver and that this may account for some of the plasma K withdrawal associated with glucose infusions. Stewart and Bourke³³ however, demonstrated large potassium losses with massive infusions of saline as well as with glucose infusions the potassium appearing in the urine.

In a more recent series of studies, Iob³⁴, Berry³⁵ and Cooper³⁶ and their associates in observing various aspects of the effect of infusions and operation on renal function and potassium balance have noted in normal subjects a high initial rate of both water and potassium excretion in the urine when infusions of either saline or glucose and water were given. The potassium excretion far exceeded 27 mEq per gram of nitrogen loss which Berry uses as catabolic expectation. After the first few hours the rate of excretion of potassium is

higher in patients immediately postthermorrhaphy than in the controls, and highest of all in a group of patients who underwent combined abdominoperineal resections. In all cases the potassium loss exceeded that expected by nitrogen output by a wide margin. It appears that controls receiving saline or 5 per cent dextrose in saline solution lost more potassium than those on glucose although variability is great.

Ariel Abels, Park and Rhoads³ reported a hypochloremic state refractory to sodium chloride administration occurring in certain surgical patients maintained on parenteral fluids following surgery for gastrointestinal cancer. These patients showed low serum chlorides, high bicarbonate levels and hypoproteinemia often with edema and hemoconcentration. They had received an average of 15 to 18 Gm of sodium chloride a day for several days before onset and showed weakness, lethargy, anorexia, nausea and a mild ileus. They responded somewhat to plasma infusions after saline solution was reduced or excluded and improved rapidly when they began to eat. It was concluded that low proteins were the cause of the syndrome. Ireneus³⁵ reported four patients with low chlorides and alkalosis, lingual dryness, distention, dehydration and oliguria and noted hypotension and a wet gray skin. These were a patient with burns, one with a pyloric obstruction and two patients with T tube drainages of the common duct who excreted large quantities of bile. Mudge and Vislocky³⁹ observed high intracellular sodium and low potassium in a patient who demonstrated a similar picture and have reported similar low potassium values in the muscles of patients suffering from renal acidosis in chronic form.

The use of potassium salts in rehydration following infantile diarrhea and potassium depleted states in diabetic acidosis and chronic nephritis has been mentioned. It is now well recognized in surgery that limitation of the use of sodium salts postoperatively is imperative. The work of Coller⁴⁰⁻⁴¹ showed that the use of isotonic sodium chloride solution resulted in marked sodium retention and very large potassium losses together with cellular dehydration and that saline solution well below isotonic concentration was far better as a replacement fluid. Moyer⁴ noted the persistence of high serum bicarbonate and low chloride in the face of sodium chloride infusions in cases in which large potassium deficits are known to occur and suggested the use of potassium salts particularly when the onset is slow and accompanied by weakness, atonia and hypotension. Similarly Maddock in a review article⁴ and Abbott⁴⁴ mentioned Darrow's work and suggested that potassium salts might prove useful clinically. Darrow⁴ suggested that potassium deficits occur when output exceeds intake with change in equilibrium as in alkalosis during rapid storage of nitrogen and under the action of adrenal cortical hormone. He predicted that many unexplained low chloride, low potassium, high bicarbonate plasma findings in various clinical conditions may prove to be potassium deficits.³⁷⁻⁴⁶

METHODS

Details of the methods and techniques employed in the metabolism unit will be reported at a later date. Serum sodium and potassium determinations in

experiment in rats, noted a rise in cell sodium with intraperitoneal bicarbonate administration. Darrow²⁸ found in rats with pyloric obstruction which were given glucose and water that serum K rose while serum Na and Cl fell as did cell sodium and chloride. On the other hand animals on diets low in chloride and low in sodium potassium and chloride showed a rise in serum bicarbonate and fall in serum chloride accompanied by a rise in cell sodium and a fall in cell potassium. Serum potassiums were low in these animals. It was also noted that cell water tended to be increased as sodium replaced potassium milliequivalent for milliequivalent.

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who had consistently high values in the range of 5.0 to 5.3 meq per liter in the absence of any demonstrable cause. In this work any plasma potassium value between 3.8 and 4.6 meq per liter is considered to be within the normal range accepting the fact that an occasional individual may show a higher value. We have encountered relatively few high levels in surgical patients and most of these were in chronic or acute renal failure as described by other workers.^{14, 51, 5, 52} Low plasma potassium values and their possible significance will be discussed later.

Potassium Values Under Controlled Metabolic Conditions—Three groups of patients were then studied in the metabolism unit. Group I consisted of patients who were fed a calculated standardized diet for fourteen days until operation and then maintained for the day of operation and four days postoperatively on parenteral fluids consisting of dextrose in saline solution, dextrose in water and 10 per cent amino acids. They illustrate the amount of potassium lost in relatively minor procedures. Fig. 2 shows the average plasma potassium values together with the average daily potassium loss in two patients C. G. with a bilateral inguinal herniorrhaphy and E. W. with a

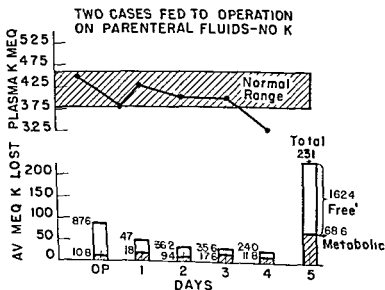


Fig. 2.—Patient in Group I on controlled diet until on ration and potassium free parenteral fluids postoperatively illustrating average plasma K level and daily and total K loss.

cholecystectomy. The average intake for these two patients was 162 meq of sodium and 149 meq of chloride ion per twenty-four hours; the electrolyte discrepancy.

preparation

metabolism unit

the regimen was designed to provide 80 Gm. of protein equivalent (13.5 Gm. nitrogen) and 18 calories per kilogram in the parenteral fluids used.

The total volume of fluid given averaged 50 cc per kilogram per day. Fig. 2 shows that these patients maintained plasma potassium levels within

urine, stool and drainages were done with a modification of the internal standard flame photometer introduced by Barnes, Richardson, Berry, Hood, and Chappell in 1946.^{47, 48} This instrument has a reproducible accuracy of 1 per cent for both sodium and potassium, and has the advantage of requiring only 1 to 2 cc of specimen. Chloride ion determinations were done by the method of Schales and Schales.⁴⁹ Bicarbonate determination was done as CO₂ content by the method of Van Slyke.⁵⁰ Nitrogen determinations were made by the Kjeldahl technique. Bloods were taken, except in emergencies in the early morning before the day's fluids or food were started. When HCO₃ was to be tested for bloods were taken under oil and allowed to clot and then all determinations were done on the serum. Sodium and potassium determinations alone were done on plasma from blood collected with careful precautions to avoid hemolysis and were placed in a 5 cc hematocrit tube containing approximately 0.1 mg sodium heparin. This was immediately centrifuged and the determinations were made on the plasma. Urines, Miller Abbott tube, and other drainages were collected as twelve or twenty-four hour specimens in covered containers. In computing outputs of water and electrolytes, care was exercised that exact measurements were made and that irrigating fluids (as in Miller Abbott tubes) were included in intake and irrigation returns included in output.

Determinations		Patients	Meq/liter
Sodium	67	32	141.00 \pm 2.63
*Potassium	71	35	4.26 \pm .43
Chloride	56	20	104.47 \pm 2.71
HCO ₃	(content)		27.6 \pm 2.0
*Three patients had consistent K values of 5.0 to 5.3 without renal or other pathology			

Fig. 1—Normal plasma values for sodium, potassium and chloride ion concentrations as determined on control subjects.

RESULTS

Normal Electrolyte Values—Preliminary normal values were obtained from a number of miscellaneous preoperative patients from the metabolic service who had no demonstrable disease other than hernia, inactive chronic cholecystitis, or nontoxic nodular goiter. Fig. 1 gives the figures obtained. These correspond closely to accepted normal values and the variation as expressed by the standard deviations is seen to be quite small. The standard deviation for the potassium value is somewhat larger because of three patients

who had consistently high values in the range of 5.0 to 5.3 meq per liter in the absence of any demonstrable cause. In this work any plasma potassium value between 3.8 and 4.6 meq per liter is considered to be within the normal range accepting the fact that an occasional individual may show a higher value. We have encountered relatively few high levels in surgical patients and most of these were in chronic or acute renal failure as described by other workers.^{14, 21, 22, 23} Low plasma potassium values and their possible significance will be discussed later.

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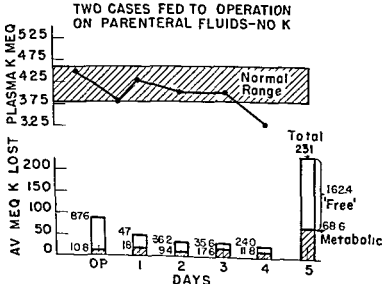


Fig. 2.—Patients in Group I on controlled diet until operation and potassium free parenteral fluids postoperatively illustrating average plasma K level and daily and total K loss.

cholecystectomy. The average intake for these two patients was 162 meq of sodium and 149 meq of chloride ion per twenty-four hours. The slight discrepancy in preparation of the regimen was calculated to contain 150 meq of sodium (nitrogen) and 15 calories per liter. The total volume of fluid given averaged 50 cc per kilogram per day. Fig. 2 shows that these patients maintained plasma potassium levels within

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the normal range until the final day when they fell slightly below normal. Also illustrated is the marked loss of potassium in the first twenty-four hours as reported by Job Berry and Cooper^{21, 22, 23} with total potassium far exceeding catabolic expectation (nitrogen in $\mu\text{mms} \times 275$). The potassium lost per day decreases in succeeding days but more potassium is lost throughout the period than is accounted for by catabolism and the total shows that the loss of potassium averaged 231 meq of which 162.4 meq represented "free" potassium, a ratio of "free" to catabolic K of 2.3 to 1.

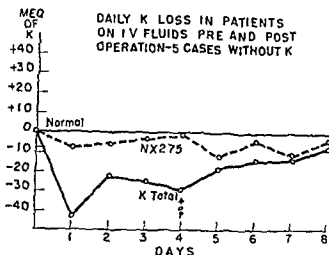


Fig. 2.—Patients in Group II on parenteral fluids for three days preoperatively, day of operation and four days postoperatively. Average daily losses of potassium together with expected losses from nitrogen balance. No potassium given.

Figs. 2 and 4 illustrate the daily potassium balance in Groups II and III patients who were placed on parenteral fluid regimens three days preoperatively after ten days of controlled oral intake on balance studies. Group II received no potassium parenterally while Group III received an average of 50.7 meq of potassium chloride parenterally per day. There were three ventral herniorrhaphies, one umbilical herniorrhaphy and one cholecystectomy in Group II (Patients M M C C A C M L and G S) while Group III consisted of four cholecystectomies, one with a common duct drainage with T tube (Patients S A A R J B and M L). All but one were women. Group II received an average of 140 meq of Na and 132.6 meq of Cl per day while Group III received 151 meq of Na, 160 of Cl and 50.7 of K. Both groups received 135 Gm of nitrogen as 10 per cent amino acids. Group II (Fig. 3) given no potassium, shows a large loss of potassium on the first day of infusions and a consistent loss diminishing with time but always exceeding that expected from nitrogen deficit. Group III given potassium (Fig. 4) shows an average loss on the first day of infusions and a loss on the day of operation and the first postoperative day and thereafter shows a slightly positive potassium balance. The figures show the average for all the cases in each group. All patients in both groups were operated upon on the fourth day.

Figs 5 and 6 show cumulative averages for the same groups and show the contrast between the debt of 170 meq averaged by Group II and the slightly positive balance achieved by Group III. The amount of potassium excretion expected on the basis of nitrogen debt was almost the same in both groups averaging 46.8 meq in the group without potassium and 49.2 meq in the potassium infused group. The large excess of potassium loss over what is accountable from catabolism is again obvious in the group which did not receive potassium. It is interesting that in these patients with relatively atraumatic procedures operation appeared to produce only a slight or transient increase in the rate of potassium excretion.

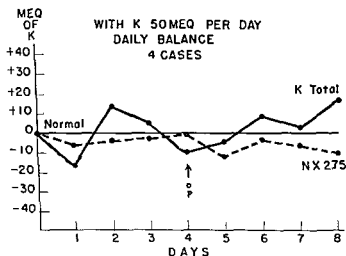


Fig 4—Patients in Group III with same program as Group II except for 0.7 meq of potassium ion per day given parenterally. Average values of daily K loss as together with expected loss from nitrogen balance.

The plasma potassium averages are shown for Groups II and III in Fig 7. The group which did not receive potassium displayed a steady fall in plasma concentration while the group receiving potassium maintained normal levels with the exception of the operative day where both pre and post operative levels were below normal. The slope of the curve off all of plasma potassium roughly parallels the deficit in the untreated group.

Potassium Equilibrium in Miscellaneous Surgical Conditions—A group of 54 patients (Group IV) were studied from the general surgical wards most of whom were subjected to major surgical procedures. Potassium determinations were done either to assist in fluid and electrolyte balance or to attempt to evaluate and correct developing imbalance. None of these patients had received any parenteral potassium or any potassium containing food or fluids by mouth since operation. Fig 8 indicates average plasma potassium levels (solid line) while the vertical bars represent highest and lowest values found. In general although not invariably acute symptoms suggestive of potassium deficiency appeared in cases with levels of 2.3 meq per liter or lower. Of 8 patients who

maintained normal potassium levels at an average of 28 days, it is interesting to note that four had gastric resections, three appendiceal abscesses, and one multiple hepatic abscesses. Clinical dehydration of moderate degree was present in some of the remaining cases but did not appear to prevent a fall in the plasma potassium level.

In addition to the loss of potassium through renal excretion, some surgical patients have an additional drain through water and electrolytes lost from the gastrointestinal tract. Figs 9 and 10 from a previous paper¹⁰ show observations that have been made on gastrointestinal tract drainages in seriously ill and often depleted patients. These values show that concentrations of electro-

Fig 5

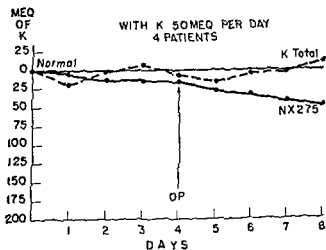
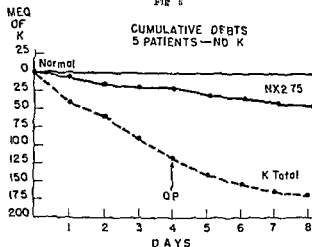


Fig 6

Fig 5—Cumulative average potassium balance and expected loss from nitrogen balance of Group II patients (Fig 3).

Fig 6—Cumulative average potassium balance and expected loss from nitrogen balance of Group III patients given Potassium (Fig 4).

lytes in fluids lost are often surprisingly hypotonic and are subject to a very wide range of variation. In general the more depleted of electrolytes the patient is the more hypotonic the secretions may be expected to be. Potassium losses from the stomach and the lower small bowel may be quite large, and doubt

Fig 7

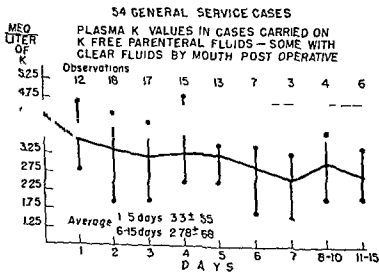
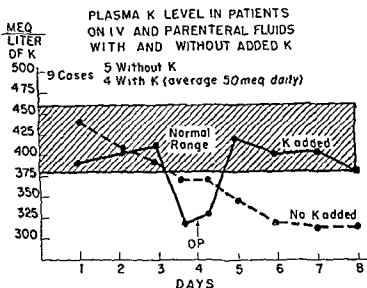


Fig 8

Fig 7 — Average plasma potassium levels of patients in Group II (dotted line) and Group III (solid line) during treatment.

Fig 8 — Patients in Group IV from General Surgical Service III, treating average plasma potassium levels and extremes observed in a group of fifty four patients who had no potassium intake following major procedure.

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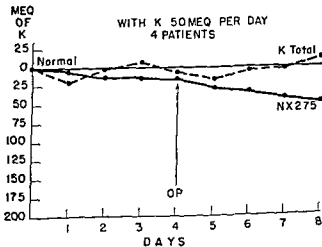
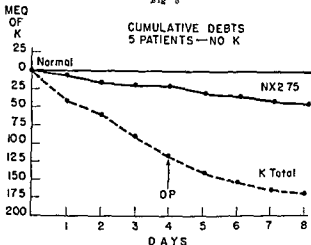


Fig 6

and expected to a from nitrogen balance
and expected loss from nitrogen balance

The symptoms that attended were very variable but in general tended to correspond to those reported by Irenius⁸ and by Aniel, Abels, Pick and Rhoads¹¹ Fig 12 shows the chemical findings in fourteen such patients (Group V), ten of whom recovered after an oral diet sometimes supplemented with potassium salts, was commenced, and four of whom had to be

Fig 11

BEHAVIOR OF PLASMA K IN PATIENTS WITH MILLER-ABBOTT TUBES, NO OPERATION, NO K

Case	DAYS							
	0	1	2	3	4	5	6	7
1	4.2	-	2.5	-				
2	4.1	-	-	-	-	3.0	-	2.8
3	-			3.1				
4	4.9	3.6	-	3.7	3.5	-	-	-
5	-	2.9	-					
6	-	3.6						
7	-	3.3	2.8	-				

A Comparison of 10 Patients Recovering on Diet, Some with Oral K and 4 Patients with Parenteral K Correction of Alkalosis

	DIET	I. V.
Days on K Free	6.0	5.0
Parenteral Fluids		
High (HCO ₃) ⁺ Average	36.5	37.3
Low Cl ⁻ Average	89.6	89.5
Average PLASMA Na ⁺	138.5	141
Average PLASMA K ⁺	2.6	2.6
Days to Normal Values	6.4	3.5

None of these patients had plasma proteins below 5.9

Fig 1*

Fig 11—Some observations of plasma potassium level in patients with Miller-Abbott tubes showing effect of parenteral fluid administration following dehydration together with large loss of fluid from the gastrointestinal tract.

Fig 1—Patient with hypochloremia and alkalosis illustrating days to operatively to onset, average plasma values and days to recovery of normal chemical values in patients who recovered on diet and those treated with parenteral potassium chloride.

less would be larger still if acute dehydration were present as well. It is easy to see how 100 meq. of potassium per day might be lost from an ileostomy or Miller Abbott tube withdrawing 3,000 to 4,000 cc. per day from the ileum. Values for normal urine are from patients in the preoperative control period on the metabolism service. The extremely low values of urinary sodium possible

Fig. 9

G I TRACT LOSSES MEQ PER LITER

	Na	K	Cl
GASTRIC (Fasting)	60.4 9-116	9.2 0.5-32.5	84.0 7.8-154.5
SMALL BOWEL (MA Suction)	111.3 82-147.9	4.6 2.3-8.0	104.2 43-137
ILEOSTOMY (Recent)	129.4 105.4-143.7	11.2 7.5-29.3	116.2 90-136.4
ILEOSTOMY (Adapted)	46	3.0	21.4
CAECOSTOMY	52.5	7.9	42.5

BILE AND PANCREATIC FISTULAE

	Na	K	Cl
BILE	148.9 131-164	4.98 2.6-12	100.6 89-117.6
PANCREAS	141.1 113-153	4.6 2.6-7.4	76.6 54.1-95.2
URINE Normal	40-90	20-60	40-120
Path	0.5-312	5-166	5-210
TRANSUDATES	130-145	2.5-5.0	90-110

Fig. 10

Fig. 9—Average figures and ranges observed for sodium, potassium, and chloride ions per liter in gastrointestinal tract fluids from 111 patients on the General Surgical Service.

Fig. 10—Average figures and ranges observed for sodium, potassium, and chloride ions from biliary and pancreatic fistulae together with averages observed in urine and transudates (Figs. 9 and 10 from Lockwood and Randall, Bull. New York Acad. Med. p. 34 April 1940).

postoperatively as well as the high potassium are of interest. Fig. 11 illustrates some observations made on patients with Miller Abbott tubes given parenteral fluids but not operated upon. These patients had intestinal obstruction and various degrees of dehydration on admission. The rapid fall in plasma potassium levels we believe reflects potassium deficiency which rapidly becomes manifest in most cases on rehydration without potassium.

Hypochloremic alkalosis—A number of the general surgical service patients were studied who developed the chemical picture of hypochloremia with alkalosis

The symptoms that attended were very variable but in general tended to correspond to those reported by Irenius²⁸ and by Amel Abels, Puck and Rhoads.²⁷ Fig 12 shows the chemical findings in fourteen such patients (Group V) ten of whom recovered after an oral diet sometimes supplemented with potassium salts was commenced, and four of whom had to be

Fig 11

BEHAVIOR OF PLASMA K IN PATIENTS WITH MILLER-ABBOTT TUBES, NO OPERATION, NO K

	DAYS							
Case	0	1	2	3	4	5	6	7
1	4.2	-	2.5	-				
2	4.1	-	-	-	-	3.0	-	2.8
3	-			3.1				
4	4.9	3.6	-	3.7	3.5	-	-	-
5	-	2.9	-					
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7	-	3.3	2.8	-				

A Comparison of 10 Patients Recovering on Diet, Some with Oral K and 4 Patients with Parenteral K Correction of Alkalosis

	DIET	I. V.
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Parenteral Fluids		
High (HCO ₃) ⁺ Average	36.5	37.3
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Fig 1—Patient with hypochloremia and alkalosis. Illustrating days postoperatively to onset, average plasma values and days to recovery of normal chemical values in patients who recovered on diet and those treated with parenteral potassium chloride

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Fig. 9—Average figures and range observed for sodium, potassium and chloride ions per liter in gastrointestinal tract fluids from 141 patients on the General Surgical Service.

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liter (with larger amounts in the urine), HCO, 37.2 meq per liter, and chloride 96.6 meq per liter in plasma. He was placed on a soft diet on the eighth day and on a regular diet on the eleventh and was able to keep up with the loss of pancreatic juice electrolytes with the aid of 6 Gm per day of enteric coated sodium chloride by mouth until the forty-sixth postoperative day, at which time the fistula was anastomosed to jejunum. He made an uneventful recovery from this second procedure and was last seen March 16 1949 having gained ten pounds in weight and feeling very well.

M. C. (79434) was a 48 year old woman, a known diabetic, who was admitted to Presbyterian Hospital Aug 11, 1948 in mild acidosis, and while in the hospital developed signs of obstructive jaundice. The common duct was explored and T tube drainage instituted. However postoperatively he developed an ileus requiring Miller Abbott tube intubation, and by the fifth postoperative day had definite signs of intraperitoneal infection localized to the right upper quadrant. The common duct was re-explored and a bile peritonitis secondary to leakage around the T tube was found. By the fourth day after the second procedure, having been given only dextrose in saline solution, dextrose in water, and some amino acids parenterally, there was moderate distention and a hematocrit of 44.5 with plasma proteins of 6.7% with a plasma HCO of 36.6 and chlorides of 90.3. The following day she was started on feedings by mouth but suddenly that evening became extremely weak listless and apathetic and was hardly able to move or speak. Blood pressure did not fall and the skin was warm and dry. Emergency electrolyte determinations at this time showed HCO, of 38.6 chlorides of 94.5, sodium of 138.5 and potassium of 1.6 meq per liter in plasma. She was given 60 meq of potassium chloride parenterally within the next twenty four hours and responded quickly with marked increase in muscular strength and vigorous objections to further parenteral fluid administration. She was able to tolerate food by mouth, and so was given supplemental potassium by mouth and made a slow but uneventful recovery, HCO, and chloride values reaching 30.6 and 97.5 meq with sodium of 138.5 and potassium of 3.6 meq per liter in the plasma by the ninth day after the acute episode.

P. J. (26666) was admitted to Presbyterian Hospital June 2 1948 with symptoms and x-ray evidence of acute intestinal obstruction which subsided promptly with Miller Abbott intubation and she was discharged on the seventh day to continue a diagnostic work up in the outpatient department. However, she returned ten days later, again with obstruction, was again decompressed with a Miller Abbott tube and a barium enema revealed a constricting lesion in the ascending colon which at operation proved to be a carcinoma. Accordingly, an ileocolicectomy and ileotransverse colostomy was done. Postoperatively she began to vomit, in spite of the tube on the third postoperative day. The tube was then withdrawn to the stomach and would not go into the duodenum again. She continued to vomit an average of 1,500 to 2,000 cc of gastric and upper small bowel contents a day for the next eight days and x-ray examination suggested a high jejunal obstruction. By the fourteenth postoperative day despite large volume of parenteral fluid the urine output had fallen to 300 cc and the following day was 200 cc with a beginning rise in serum urea nitrogen. She was mildly edematous, extremely uncomfortable and vomited and had lost through the Miller Abbott tube a total of 3,600 cc without oral intake. Plasma sodium was 141.5 meq per liter and potassium 2.4 meq per liter with HCO, 34 meq per liter and chlorides 94.7 meq per liter. Hematocrit was 42.4 and plasma proteins 8.38 Gm. per cent. She therefore represented a picture of dehydration oliguria and peripheral edema with low plasma potassium alkalemia and mild hyponatremia. A blood volume done this day showed a total volume of 2,000 cc per kilogram body weight with 29 cc red cells and 41 cc plasma. A plan was therefore made to rehydrate her, replace as much of the potassium deficit as possible and then re-tore the blood volume by transfusion before re-operating to discover the cause of the upper small bowel obstruction. Through a misunderstanding only 4,300 cc of parenteral fluids were given the following (fifteenth postoperative) day and as a result she excreted only 240 cc of urine in the following twenty four hour period. She was given 2,000 cc of a mixture of potassium and sodium chloride containing a total of 60 meq of K, 1,300 cc of

maintained on parenteral fluids and who responded to the intravenous administration of potassium chloride. The number of days between operation and the establishment of the chemical diagnosis was very similar in the two groups as were the low chloride and high bicarbonate findings. All of these patients had been generously infused with sodium chloride, some with excessive amounts and all had developed hyponatremia and alkalosis in spite of or in part because of, such therapy. It should be noted that the average plasma sodium levels were within normal range and that the plasma potassium levels were low. None of these patients presented a marked hypoproteinemia. Three cases presented briefly will illustrate certain of these points.

CASE REPORTS

W. A. (020999) was a 59 year old man who was admitted to the Presbyterian Hospital Aug. 26 1948 with a chief complaint of 2½ months of increasing jaundice and pruritis, anorexia, and a weight loss of fifteen pounds. Past history was noncontributory, there was no history of fatty food intolerance or previous jaundice. Laboratory workup revealed no anemia, a serum bilirubin of 9.6 mg. per cent and alkaline phosphatase of 10 Bodansky units. Hematocrit was 43% and serum proteins 7.13 Gm. per cent. Cephalin flocculation was negative. Duodenal drainage revealed no bile and no blood cells. X-ray examination showed a postbulbar constriction of the duodenum. The patient had consistently clay colored stools and dark urine and was clinically jaundiced. Exploration was carried out on Sept. 3 1948, and a carcinoma of the ampulla of Vater involving the common duct and part of the head of the pancreas was found. A pancreaticoduodenectomy with choledochojunostomy and gastrojejunostomy was performed. A sump drain was placed to the cut end of the pancreas in view of the fact that no ducts could be found and the marked edema of the pancreas prevented anastomosis to the jejunal loop. The procedure was well tolerated, and on the operative day the patient was given a total of 2,300 cc. of blood and 1,500 cc. of saline solution. A nasogastric tube was placed and postoperatively drained 2,800, 2,100, 500 and 3,600 cc. in the first four postoperative days. Of this about one half was water taken by mouth. The patient was maintained on a parenteral infusion intake averaging 3,200 cc. per day of which in the first three days 1,500 cc. per day were saline solution and on one occasion 500 cc. of M/6 sodium lactate were given. Urine output was satisfactory, averaging 1,300 cc. per day. By the fourth postoperative day the patient complained of marked thirst yet vomited around the tube when he took water by mouth. He was drowsy, and had a sanguineous drainage with plasma proteins CO 38.3 meq. per liter of sodium and 14.9 meq. per liter of potassium, and the drainage from the wound 10.0 meq. per liter of

and 60 meq. per day for the two succeeding days together with an intake of sodium chloride in a total volume of 3,500 cc. since the fistula had begun to drain large volumes of pancreatic juice. The following day he considerably improved, nasogastric drainage had dropped to 2100 cc. with an oral intake of 1,600 cc. of water and plasma sodium had fallen to 131 meq. per liter with plasma potassium remaining at 2.5 meq. per liter. Chloride had risen to 90 meq. per liter and bicarbonate had fallen to 29.8 meq. per liter. The following day (sixth postoperative) the serum sodium was 130 meq. per liter, potassium 2.9 meq. per liter, HCO₃ 27.2 meq. per liter and chloride 93 meq. per liter. There was drainage of 1,000 cc. of pancreatic juice and the urinary output was 1,000 cc. which contained but 9.3 meq. of the 60 meq. of potassium administered. He retained most of an oral intake of full fluids with nasogastric tube clamped and the following day the tube was removed. By the seventh day the serum sodium was 137 meq. per liter potassium 4.1 meq. per

liter (with larger amounts in the urine), HCO_3 , 27.2 meq per liter, and chloride 86.6 meq per liter in plasma. He was placed on a soft diet on the eighth day and on a regular diet on the eleventh, and was able to keep up with the loss of pancreatic juice electrolytes with the aid of 6 Gm per day of enteric coated sodium chloride by mouth until the forty-sixth postoperative day at which time the fistula was anastomosed to jejunum. He made an uneventful recovery from this second procedure and was last seen March 16, 1949 having gained ten pounds in weight and feeling very well.

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Accordingly an ileostomy and a neotransverse colectomy was done. Postoperatively she began to vomit in spite of the tube on the third postoperative day. The tube was then withdrawn to the stomach and would not go into the duodenum again. She continued to vomit an average of 1,500 to 2,000 cc of gastric and upper small bowel contents a day for the next eight days and x-ray examination suggested a high jejunal obstruction. By the fourteenth postoperative day despite large volumes of parenteral fluids, the urine output had fallen to 350 cc and the following day was 200 cc with a beginning rise in serum urea nitrogen. She was mildly edematous, extremely uncomfortable and vomited and had lost through the Miller Abbott tube a total of 3,000 cc without oral intake. Plasma sodium was 141.5 meq per liter and potassium 2.4 meq per liter with HCO_3 , 34 meq per liter and chlorides 94.1 meq per liter. Hematocrit was 42.4 and plasma proteins 8.38 Gm per cent. She therefore represented a picture of

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maintained on parenteral fluids and who responded to the intravenous administration of potassium chloride. The number of days between operation and the establishment of the chemical diagnosis was very similar in the two groups, as were the low chloride and high bicarbonate findings. All of these patients had been generously infused with sodium chloride, some with excessive amounts, and all had developed hyponatremia and alkalosis in spite of, or in part because of, such therapy. It should be noted that the average plasma sodium levels were within normal range and that the plasma potassium levels were low. None of these patients presented a marked hypoproteinemia. Three cases presented briefly will illustrate certain of these points.

CASE REPORTS

W. A. (920899) was a 58 year old man who was admitted to the Presbyterian Hospital Aug. 26, 1948 with a chief complaint of 2½ months of increasing jaundice and pruritis, anorexia and a weight loss of fifteen pounds. Past history was noncontributory. There was no history of fatty food intolerance or previous jaundice. Laboratory work up revealed no anemia, a serum bilirubin of 9.6 mg. per cent and alkaline phosphatase of 107 Bo lansky units. Hematocrit was 43.5 and serum proteins 7.13 Gm. per cent. Cephalic flocculation was negative. Duodenal drainage revealed no bile and no blood cells. X-ray examination showed a postbulbar contraction of the duodenum. The patient had consistently clay colored stools and dark urine and was clinically jaundiced. Exploration was carried out on Sept. 3, 1948 and a carcinoma of the ampulla of Vater involving the common duct and part of the head of the pancreas was found. A pancreaticoduodenectomy with choledochojejunostomy and gastroyejunostomy was performed. A sump drain was placed to the cut end of the pancreas in view of the fact that no ducts could be found and the marked edema of the pancreas prevented anastomosis to the jejunal loop. The procedure was well tolerated, and on the operative day the patient was given a total of 2,300 cc. of blood and 1,500 cc. of saline solution. A nasogastric tube was placed and postoperatively drained 2,400, 2,100, 5,200, and 3,600 cc. in the first four postoperative days. Of this about one half was water taken by mouth. The patient was maintained on a parenteral infusion intake averaging 3,000 cc. per day, of which in the first three days 1,500 cc. per day were saline solution and on one occasion 500 cc. of M/G sodium lactate were given. Urine output was satisfactory, averaging 1,300 cc. per day. By the fourth postoperative day the patient complained of marked thirst yet vomited around the tube when he took water by mouth. He was drowsy, mildly distended, uncomfortable and showed a moderate amount of sero sanguineous drainage.

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14.8 meq per liter of potassium and the drainage from the wound 10.25 meq per liter of Na and 1.9 meq of K per liter. It was decided that he had a potassium deficiency probably with an associated chloride deficiency as the result of the gastric and upper small bowel suction. Accordingly he was started on a regime which gave him 30 meq of KCl that day and 60 meq per day for the two succeeding days together with an average of 2.0 meq of sodium chloride in a total volume of 3,500 cc. since the fistula had begun to drain large volumes of pancreatic juice. The following day he considerably improved, nasogastric drainage had dropped to 2,100 cc. with an oral intake of 1,600 cc. of water, and plasma sodium had fallen to 131 meq per liter with plasma potassium remaining at 2.5 meq per liter. Chloride had risen to 90 meq per liter and bicarbonate had fallen to 29.8 meq per liter. The following day (4th postoperative) the serum sodium was 130 meq per liter.

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the appearance of a marked potassium deficit as has been demonstrated so well by Darrow⁴ in the rehydration of infants dehydrated by diarrhea, as well as by Butler¹¹ and others^{11, 12, 13} in rehydration in diabetic acidosis.

Darrow⁴ has suggested that changes in equilibrium result in potassium deficiency, and has demonstrated in experimental animals that induced alkalosis¹⁴ results in lowered cell potassium with a direct relationship existing between the amount of sodium in the cell and the plasma bicarbonate. Changes in equilibrium certainly occur in pyloric obstruction, where chloride ion loss predominates, in biliary or pancreatic fistulas where sodium loss is dominant, in large volume losses from the small bowel or as diarrhea. Disturbances may also occur in the postoperative period through depression of renal function with sodium retention as described by Collier¹⁵ in which connection we have noted postoperative sodium excretion levels as low as 0.5 meq per liter of urine in spite of normal plasma sodium levels and with simultaneous high levels of K excretion.

Gastrointestinal tract losses may be a primary route of a considerable loss of potassium as we have previously reported¹ and are illustrated in Figs 9 and 10 and surgical patients often have large volumes of gastrointestinal tract losses with dehydration. The extent of these losses is well illustrated by Abbott, Mellors and Muntwyler in experimental work with dogs¹⁶ and in diarrhea studies by Butler¹¹ and Darrow^{4, 6, 7}.

Long and traumatic surgical procedures appear to be followed by an increase in potassium losses as compared to those occurring in hemorrhaphies or in normal subjects on infusions as studied by Perry¹⁷ and Cooper¹⁸. Thus the surgical patient may have many simultaneous factors operating to produce losses in potassium which may reach considerable magnitude.

In the studies on patients from our metabolic unit it will be noted that we have confirmed the reports of Job and her associates¹⁹ that in minor surgical procedures at least placing a patient on parenteral fluids has more of an effect on potassium loss than does the operation itself. Fig. 3 (Group II) shows the large loss in the first twenty-four hours with smaller but definite losses throughout the period. Operation on the fourth day produced a slight increase in the loss but it did not reach the magnitude of that of the first day on infusions. As reported by Perry¹⁷ and others the amount of potassium lost far exceeds that expected from the ratio of nitrogen to potassium in cells. We have used a figure of 275 meq of potassium per gram of nitrogen as a compromise between 257 calculated from days 2 to 11 in Benedict's data¹ and the lower figures discussed by Perry.¹⁷ In Group II patients who did not receive potassium the ratio of unassociated potassium is 2.6 to 1 of potassium associated with nitrogen loss. This checks well with 2.3 to 1 noted in the Group I patients who were carried on parenteral fluids only from operation on as described in Fig. 2.

The administration in infusions of 50 meq of K a day as potassium chloride made a striking difference in the potassium balance of similar groups of patients as can be seen by comparing metabolic Groups II and III (Figs

saline solution, and 1,000 cc of an amino acid mixture containing 34 meq of sodium chloride per liter

The sixteenth day he was given 6,000 cc parenterally including 3 liters of sodium potassium chloride mixture, 1,000 cc of dextrose in saline solution, 1,000 cc of amino acids, and 1,500 cc of 5 per cent dextrose in water. She received 90 meq of K. In the next twenty-four hour period she voided 1,360 cc of urine, and serum sodium was 136.5 meq potassium 2.9 meq chloride 101.2 and HCO_3^- 27.2 meq in plasma. She was then carried on maintenance fluids of from 3,500 to 4,000 cc of parenteral fluids a day for the next three days and was given three blood transfusions to restore the blood volume. She voided 2,800 cc, 1,750 cc and 1,950 cc in the next three days and the edema disappeared. This was accompanied by a fall in hematocrit and plasma protein to 40 and 6.97 respectively on the eighteenth day. She was given an average of 20 meq of K per day during this period, which was not enough for her plasma K which was 3.9 meq per liter on the eighteenth day fell to 2.4 on the twentieth day together with drop in urine output to 650 cc and a rise in hematocrit to 46.1, with proteins of 7.8 Gm per cent. This was treated with an additional amount of parenteral fluids and 90 meq of K, and on the twenty-first postoperative day exploration was carried out again and an intussusception of the proximal jejunum found and resected. An end to end anastomosis and gastrojejunostomy were performed. It was noted that the bowel, which had been generally edematous at the first operation was much less so at the second. One liter of blood but no plasma was given the operative day and the following morning plasma sodium was 128 meq potassium 3.0, and chloride 91.8 meq. The Miller Abbott tube which had been placed past the jejunal anastomosis drained 2,000 cc and in addition she vomited 500 cc the first postoperative day. The hematocrit was 51.5 and plasma proteins 6.5, serum sodium 132 and potassium 4.0 meq per liter. She was given 30 meq of K this day with 5,000 cc of water, 2,000 of it saline solution, and the following two days was given 90 meq of potassium in 3 liters of potassium and sodium

potassium 2.6 meq chloride 91.9 and HCO_3^- 28.7 meq per liter. She put out 2,000 cc and 2,750 cc of urine on the fifth and sixth postoperative days, and on the sixth day having received 27,000 cc of parenteral fluid and 2.0 meq of potassium since operation, the plasma sodium was 140 meq potassium 3.0 meq chloride 93.4 meq and HCO_3^- 24.2 meq per liter. Hematocrit was 48 and plasma proteins 5.77. She was started on fluids by mouth on the seventh postoperative day the tube was taken out the ninth day and she went home on the twentieth day. She has remained well since that time.

DISCUSSION

It is obvious from a review of the literature that many of the conditions which have been reported as leading to potassium deficiency states can and often do exist in surgical patients. Losses as the result of reduction or elimination of potassium intake through the gastrointestinal tract are almost the rule and if one adds the effects of infusions^{21,22} with increased excretion of potassium and its possible withdrawal in glycogenesis as well as the effects of saline solution in increasing potassium losses as observed by Stewart and Bourke²³ and Job²⁴ almost every postoperative surgical case becomes a candidate for potassium deficiency. Dehydration is certainly present at some time in many surgical conditions and as Elkinton and Winkler and their associates have shown^{25,26,27,28,29} potassium losses are very large in dehydration, and in the presence of excess sodium²⁹ the potassium being excreted by the kidney as it is moved out with intracellular water and often displaced by sodium within the cell. Subsequent rehydration with saline solution results in

the appearance of a marked potassium deficit as has been demonstrated so well by Darrow⁸ in the rehydration of infants dehydrated by diarrhea as well as by Butler¹⁰ and others^{11, 12, 13} in rehydration in diabetic acidosis.

Darrow¹⁴ has suggested that changes in equilibrium result in potassium deficiency, and has demonstrated in experimental animals that induced alkalosis⁷ results in lowered cell potassium with a direct relationship existing between the amount of sodium in the cell and the plasma bicarbonate. Changes in equilibrium certainly occur in pyloric obstruction, where chloride ion loss predominates in biliary or pancreatic fistulas where sodium loss is dominant, in large volume losses from the small bowel or as diarrhea. Disturbances may also occur in the postoperative period through depression of renal function with sodium retention as described by Collet¹⁵ in which connection we have noted postoperative sodium excretion levels as low as 0.5 meq per liter of urine in spite of normal plasma sodium levels and with simultaneous high levels of K excretion.

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Laboratory and traumatic surgical procedures appear to be followed by an increase in potassium losses as compared to those occurring in hemorrhaphies or in normal subjects on infusions as studied by Berry²⁵ and Cooper.²⁶ Thus the surgical patient may have many simultaneous factors operating to produce losses in potassium which may reach considerable magnitude.

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DISCUSSION

It is obvious from a review of the literature that many of the conditions which have been reported as leading to potassium deficiency states can and often do, exist in surgical patients. Losses as the result of reduction or elimination of potassium intake through the gastrointestinal tract are almost the rule and if one adds the effects of infusions^{21, 22} with increased excretion of potassium and its possible withdrawal in glycogenesis as well as the effects of saline solution in increasing potassium losses as observed by Stewart and Bourke²³ and Ish²⁴ almost every postoperative surgical case becomes a candidate for potassium deficiency. Dehydration is certainly present at some time in all surgical conditions and as Elkinton and Winkler and their associates have shown^{25, 26, 27, 28} potassium losses are very large in dehydration and in the presence of excess sodium²⁹ the potassium being excreted by the kidney as it is water cut with intracellular water and often displaced by sodium within the cell. Subsequent rehydration with saline solution results in

More commonly, however, we have seen a rather diffuse symptom complex resembling that described by Ariel, Abels, Pack, and Rhoads³⁷ and Ireneus,³⁸ consisting of the onset from the fourth to the ninth postoperative day of drowsiness, languor, chronic ileus with moderate distention, anorexia and weakness, frequently accompanied by some peripheral edema, oliguria, and hemocoencetration. Not all symptoms are present in any one case and it is evident that the pattern is not altogether specific. Usually accompanying this syndrome are a low plasma chloride, high plasma bicarbonate and a low plasma potassium. It has been noted by Ariel that these patients improve rapidly when they begin to eat and Fig. 12 documents fourteen such patients (Group V), ten of whom (including M. C.) recovered on diet, some with supplemental potassium. The increase in dietary intake in these patients is usually slow, and it was observed that the time required for chemical restoration of normal bicarbonate and chloride levels averaged 64 days after food was started. Four patients, including P. J. had to be carried on parenteral fluids and responded symptomatically and chemically to the parenteral administration of from 60 to 90 meq. of potassium per day, thus leading to the conclusion that hypochloremic alkalosis is in some way associated with potassium deficiency and is in large part a primary potassium deficiency state. We have been using potassium containing solutions on the surgical service at Presbyterian Hospital for a little more than one and one half years and employ two solutions. The first of these consists of 110 meq. of sodium, 30 meq. of potassium and 140 meq. per liter of chloride ion in distilled water*. The second consists of 30 meq. of potassium and 30 meq. of chloride ion per liter in 5 per cent dextrose and water (2.2 Gm. KCl per liter) and was developed on the surgical service to fulfill the need for a solution containing potassium but not sodium. Both are administered by standard infusion equipment at a rate not exceeding 1 liter per hour with care being exercised to see that the infusion does not run in a steady stream when first started. We have not exceeded this concentration of potassium although Darrow⁹ has used 40 meq. per liter and routinely uses 30 meq. per liter.

Certain specific contraindications to the use of these solutions are observed. The solutions are not used in acutely dehydrated patients until rehydration is well under way, the hematocrit is falling and urinary output is definitely rising unless (as was the case with patient P. I.) we have laboratory evidence to show that the patient has a low plasma potassium level. We do not use the solutions in patients with acute or chronic renal disease unless the serum potassium is low and the indications are definite, and then only with great caution. Furthermore solutions of potassium are not used during or for twenty-four hours after major operative procedures. Following these precautions we have not observed any evidence of potassium intoxication and the solutions are now in general use on the surgical service.

Therapeutic administration consists of the use of from 60 to 120 meq. of potassium a day with due regard to the total fluid volume permissible in

(* 2.2 Gm. KCl, 6.4 Gm. NaCl per liter). This solution was first introduced to the hospital by Dr. G. H. Muller of the Medical Service.

3, 4, 5, and 6) Potassium losses occurred only during the first twenty four hours, the day of operation, and the first postoperative day in Group III as shown in Fig. 4, and the cumulative balance was actually positive for potassium during the eight days. The nitrogen losses, however, were unaffected and are very similar for the two groups. This dissociation of nitrogen loss and potassium balance suggests that potassium sodium relationships are more significant under these circumstances. Unfortunately muscle biopsies have not been done with initial controls to confirm that intracellular sodium actually decreased in the potassium treated patients as seems probable.

We have been particularly interested to see whether plasma potassium values which are easily obtained would be of value in estimating potassium deficit. It seems definite that there is a drop in the plasma potassium levels in the patients receiving no potassium that did not occur in patients who received parenteral potassium in prophylactic amounts. Fig. 7 shows the comparative figures for Groups II and III. In Group II patients the amount of potassium excreted unassociated with N losses decreases with time and it appears that they tend to level off at a lower plasma level and may not develop signs of acute potassium deficiency even during an extended period on parenteral fluids. However, when more major procedures are involved and dehydration gastrointestinal tract losses or perhaps the injudicious use of saline solution enters the picture together with a reduction in the capacity of the kidney to maintain balance some patients have potassium losses which are very large and develop signs of acute deficiency. Fig. 8 shows the trend and extremes of plasma potassium levels in a series of patients from the general ward service. It will be noted that plasma potassium concentrations some times reached levels representing a reduction of 60 to 70 per cent of normal values. In general it may be stated that symptoms and chemical findings of imbalance seem to appear at levels of 3.0 meq. and that the more severe expressions of deficiency appeared with levels of 2.6 meq. per liter or less. The two cases of extreme muscular weakness that we have observed (one of whom M. C. is briefly reported upon) had levels at the time of the weakness of 2.0 or below. However, there seems to be considerable variation in the level at which any particular patient will manifest symptoms so the plasma potassium level becomes a definitive index of significant deficiency only when below 2.6 meq. per liter even though levels below 3.5 meq. per liter may be suggestive. Fig. 11 shows that efforts to rehydrate a patient with dehydration associated with continuing gastrointestinal losses may result in low plasma potassium levels in the absence of potassium replacement.

The symptoms of potassium deficiency are divisible into two groups. The first of these is the acute syndrome of skeletal muscle weakness sometimes with paralysis of the intercostals and diaphragm as described by Holler¹¹, Martin and Wertman¹² and Nicholson and Brunning¹³ in diabetic acidosis with rehydration and by Brown, Currens and Marchand¹⁰ in chronic nephritis. This syndrome has been observed by us in two patients and perhaps in early stages in two more. The patient M. C. illustrates this manifestation.

been demonstrated to occur. However the management of potassium requirements must always be integrated with an over all program of physiologic water and electrolyte replacement.

SUMMARY

The potassium balance and serum potassium levels were studied in three groups of patients observed in a surgical metabolism unit. One group was maintained on food by mouth until operation and then carried on parenteral fluids including amino acids but without added potassium for the operative day and four days thereafter. The second group was placed on the same parenteral fluids including amino acids but these were given for three days preoperatively as well as postoperatively. The third group was similar to the second except for the addition of 50 meq of potassium per day parenterally. The first two groups demonstrated a consistent loss of potassium in excess of that associated with nitrogen. The largest losses occurred on the first day on parenteral fluids. Operation increased the potassium loss in the second group on the operative and first postoperative days but the magnitude of the losses was below that occurring on the first day of parenteral fluid therapy. The third group given potassium showed losses on the first day of parenteral fluids and on the operative and first postoperative days but maintained a positive potassium balance for the period. Plasma potassium levels fell below normal in the second group but not in the third except for the operative day.

Data are presented for a miscellaneous group of surgical cases in which postoperative plasma potassium levels were observed. There was wide variability but a marked fall below normal in most cases. It is suggested that marked deviations in the plasma potassium level may serve as an approximation of the degree of potassium deficit.

Data are presented from fourteen cases of hypochloremic alkalosis together with brief reports of three cases. It is shown that this condition responds both to oral intake of food and to the parenteral administration of potassium chloride although it is refractory to and made worse by sodium chloride. The features of this syndrome are discussed and it is concluded that hypochloremic alkalosis is probably a potassium deficiency state.

The therapeutic and prophylactic uses of potassium salts in certain surgical conditions are discussed and methods and precautions in their administration are outlined.

The authors would not have been possible without the valuable assistance of the nursing and technical staff of the Surgical Metabolism Unit including Miss Florence Schorske, Miss Rita Litten, Miss Emily Cragin, Mrs. Julia Carter, Miss Helen Landelaki, Miss Charlotte R. Harwood and Miss Edith Lombard.

REFERENCES

1. Penick F. C. A Study of Intragastric Feeding. Publication 203, Washington D. C. The Carnegie Institution of Washington.
2. Crumley L. L., Hoar C. S. and Tinsell F. F. The Metabolism of Fixed Acid During Fasting. *J. Biol. Chem.* 57: 3-19, 1923.
3. Butler A. M., McKhann C. F. and Crumley J. L. Intracellular Fluid Loss in Diarrheal Disease. *J. Lab. Invest.* 3: 54-59, 1923.
4. Darrow D. C. Congenital Alkalosis With Diarrhea. *J. Pediatr.* 26: 519-53, 1945.

the patient being treated. Such amounts are given to patients with documented electrolyte imbalance and low serum or plasma potassium levels, particularly those that demonstrate hypochloremia and a high serum bicarbonate. Similar levels of administration are sometimes necessary to replace potassium lost in extensive drainage from the gastrointestinal tract through Miller Abbott tube or fistula and an effort is made in these cases to determine the twelve or twenty-four hour losses from all sources and quantitatively to replace sodium, potassium chloride and bicarbonate ions. In these cases the flame photometer is essential for rapid and accurate determinations of concentrations. Plasma and urine potassium levels are recorded daily, and as these rise the amount of potassium administered is accordingly reduced.

In the past year we have been using potassium solutions prophylactically starting the second postoperative day in patients that we expect to carry on parenteral fluids for four or more days with not more than clear fluids by mouth and by this means we appear to have reduced the number of patients who have developed edema and alkalosis and we have certainly improved potassium equilibrium in these patients. On these grounds we feel that such a program has a rational basis and will be increasingly useful. However it is agreed that further work is needed before routine prophylactic use of potassium can be advised. The amount administered prophylactically is usually 30 meq of potassium per day. Rigid limitation of sodium infusions is an important part of preventing potassium depletion and edema since excessive sodium displaces intracellular potassium and saline solution is restricted to a maximum of 500 cc per day unless there are definite indications for the use of more than this amount. In this connection the recommendations of Collier and his associates¹⁰ are generally observed.

We have found very useful for oral therapy a mixture of potassium acetate bicarbonate and citrate 1 Gm of each made up to a volume of 8 cc with water. Such a mixture contains 27 meq of potassium in 8 cc and can be given in doses of 4 cc three times a day well diluted in fruit juice to supplement the potassium intake of patients who are tolerating fluid feedings. This sometime eliminates the necessity for infusions.

Low plasma potassium levels are accompanied by definite electrocardiographic changes in man as reported by Holler¹¹ and Prown. Currens and Marchand.⁹ Darrow and Miller¹² have shown definite pathologic changes in the heart muscle of rats with low serum potassium and alkalosis as the result of desoxycorticosterone administration. No definite pathologic changes attributable to potassium deficiency are known to occur in patients other than edema of cells in which sodium has replaced potassium but it is reasonable to assume that changes take place in cells as the result of the marked water and electrolyte imbalances that have been observed of which potassium deficiency constitutes an important part. We feel that the therapeutic and prophylactic use of potassium salts in certain surgical conditions will probably be increasingly indicated to replace or anticipate deficits which have

3. Fern W O The Deposition of Potassium and Phosphate With Glycogen in Rat Livers J Biol Chem 128 297 1939
- 31 Stewart, J D and Rourke G M The Effects of Large Intravenous Infusions on Body Fluid J Clin Investigation 21 19 1942
- 34 Job, V Berry R F L and Campbell K N Excretion of Potassium in the Immediate Postoperative Period Univ Hosp Bull Ann Arbor 14 57 1948
- 35 Berry R F L, Job V, and Campbell K N Potassium Metabolism in the Im
- 36 Coop
- 37 Arie
- 38 Irene 592 1945
- 39 Mulg d Muscle in
- 40 Collei Postopera
- 41 A Translocation in Salt Solution in
- 42 84 536 1947
- 43 Fat, and Vitamins
- 44 Arch Surg 57 523 1948
- 44 Abbott W F Fluid, Electrolyte and Nutritional Problems in Surgery S Clin North America 26 1359 1946
- 45 Darrow D C Body Fluid Physiology The Relation of Tissue Composition to Problems of Water and Electrolyte Balance New England J Med 233 91, 1945
- 46 Darrow D C Tissue and Water Electrolyte, Ann Rev Physiol 6 95, 1946
- 47 Barnes R B Richard on D Berry, T W and Hood, P L Inlast & Enam Chem (Analytical Ed) 17 605 1945
- 48 Berry J W Chappell D G and Barnes P B Improved Method of Flame Photometry Inlast & Enam Chem (Analytical Ed) 18 17 1946
- 49 S F for the Determination
- 50 Van Bicarbonate Concentration as a Measure
- 51 Lin Clinical Syndrome of Potassium In
- 52 toxication Am J Med 4 33 1947
- 53 Covan C D and Wirth W M Pot
- 54 Keith N M and Osterberg A E Efficiency A Study of Ten Ca
- 55 Werner S C Habib D Y Partial of the Effects of Controlled (Operation (In Press)
- 56 Lockwood T C and Randall H T The Place of Electrolyte Studies in Surgical Patients Bull New York Acad Med 25 229 1949
- 57 Abbott W F Mellor R C and Muntwiler F Fluid Protein and Electrolyte Alteration in Experimental
- 58 Darrow D C and Miller H C Injection of the oxcorticoi
- 59 Miller H C and Darrow D C Serum Potassium and to the Toxic Effects of Ingested Potassium Chloride Am J Physiol 130 747 1940

- 5 Gamble J L, Fahey K R, Appleton J, and MacLahlin, R Congenital Alkalosis With Diarrhea J Pediatr 26 509 1945
- 6 Darrow D C The Retention of Electrolyte During Recovery From Severe Dehydration Due to Diarrhea, J Pediatr 28 517 1946
- 7 Cowan C D Jr, and Darrow D C The Use of Isotonic Chloride in the Treatment of Dehydration 1933
- 8 Dinan A, T Hull, I M and Peters John I Sodium Potassium and H₂O in the Cells and Serum of Blood in Diabetic Acidosis Am J Physiol 149 667, 1948
- 9
- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19 Elkinton T R Winkler A W and Danowski P S Transfer of Cell Na and K in Experimental and Clinical Conditions, J Clin Investigation 27 74 1948
- 20
- 21
- 22
- 23 Willson, D M Lower M₂ and M₃ and M₄ in a Case of Cushing's Syndrome Metabolic Study J Clin Investigation 19 701, 1940
- 24 Iannetti H and Darrow D C The Effect of Depletion of Extracellular Electrolytes on the Chemical Composition of Skeletal Muscle Liver and Cardiac Muscle, J Biol Chem 134 721 1940
- 25 Iannetti H The Effect of Alkalosis in the Chemical Composition of Brain Skeletal Muscle Liver and Heart, J Biol Chem 136 1 1940
- 26 Darrow, D C Changes in Muscle Composition in Alkalosis J Clin Investigation 25 34 1946
- 27 Darrow, D C Schwartz R Iannetti J F and Coville E The Retention of Serum Bicarbonate Concentration to Muscle Composition J Clin Investigation 27 194 1948
- 28 Kuhlmann D Ragan C Ferrellee J W, Atchley D W and Loeb R F Toxic Effect of Desoxycorticosterone Esters in Dogs Science 90 496 1937
- 29 Ferrellee J W Parker D Carne W H Gerits M K Atchley D W and Loeb R F Certain Effects of Desoxycorticosterone Development of Diabetes Insipidus and Replacement of Muscle Potassium by Sodium in Normal Dog, Am J Physiol 135 250 1941
- 30 Hastings A B and Fitchelberger J The Exchange of Salt and Water Between Muscle and Blood I The Effect of an Increase in Total Body Water Produced by the Intravenous Injection of Isotonic Salt Solution J Biol Chem 117 1 1937
- 31 Block F V Bollman J L Mann F C and Kendall E C The Effect of the Intravenous Injection of Glucose and Other Substances on the Concentration of Sodium in the Serum of the Dog J Biol Chem 125 57 1938

- 1 Adequate amounts of all nutritional elements
- 2 Inexpensive and easy to prepare
- 3 Easily digested and absorbed with low residue
- 4 Drips easily by gravity
- 5 Not too high salt or osmotic concentration
- 6 Relatively stable in refrigerator for 48 hours

The Scott Ivy pabulum⁹ has been widely advocated^{2, 4} because of its comprehensive nutritional composition. Nevertheless, even in the experience of its advocates⁴ it tends to cause diarrhea and cramps requiring paregoric or its equivalent. The Hollander formula¹⁰ one of the best devised may produce diarrhea when first used if the quantity is sufficient to maintain nutrition even though jejunal tolerance may eventually develop. Although they are nutritionally complete the fact that there are thirteen constituents in the Scott Ivy pabulum⁹ and twelve in the Hollander formula¹⁰ renders it unlikely that they will be easily prepared by the average hospital kitchen staff. By way of contrast Allen¹¹ has found a simple mixture of equal parts of milk and lime water given in small quantities to be well tolerated by the jejunum even in the first few days but it is difficult to administer an adequate caloric content to maintain nutrition using this mixture alone.

The single food which most nearly seemed to meet Stewart's requirements⁸ for an ideal feeding mixture was whole milk. Milk is universally available of moderately high caloric value almost complete nutritionally and inexpensive. Recent investigators^{4, 10} have avoided the use of milk as a base for jejunostomy feedings because of the apparent intolerance of the jejunum to the fat in whole milk. In preliminary investigations an attempt was made gradually to increase jejunal tolerance to the fat in whole milk by starting the feeding with skim milk and adding increasing proportions of whole milk. The milk was peptonized to increase its digestibility.⁷ Three out of the five patients on whom this system was used developed severe diarrhea and abdominal cramps by the time they were receiving whole milk. This seemed to be an adequate demonstration that it was impractical to introduce undiluted whole milk directly into the jejunum in sufficient amounts to maintain nutrition in the average patient.

Since it was assumed that the fat in the milk was producing the diarrhea attention was next turned to this aspect of the problem and to the theories of fat absorption mechanisms. The generally accepted lipolytic theory of fat absorption (Fig. 1) assumes that all fat ingested in the diet is completely hydrolyzed by pancreatic lipase to glycerol and fatty acids. The fatty acids are then supposed to conjugate with bile salts to form a water soluble fatty acid bile salt complex which is absorbed through the membrane of the cells of the intestinal mucosa. In these cells resynthesis is thought to occur to form phospholipids and triglycerides which pass both through the lymphatics and via the thoracic duct to the blood stream and through the portal vein to the liver. Collaborators from the Department of Physiological Chemistry assisted in determining whether the work of Frazer¹² dealing with fat absorption as related to particle size might be applicable to this problem.

OBSERVATIONS IN JEJUNAL ALIMENTATION

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A CRITICAL feature of the management of patients facing radical surgery is the correction of malnutrition if it exists and the active maintenance of adequate feeding.¹ There are four possible ways of accomplishing these aims: (1) Oral ingestion of a suitable diet, (2) gavage feeding through an orally introduced rubber tube whose tip lies either in the stomach or in the upper jejunum, (3) parenteral feedings through a vein or the subcutaneous tissues, (4) feeding into a surgically constructed jejunostomy. With our present day facilities it is next to impossible to satisfy basic nutritional requirements by parenteral means alone. It is generally agreed that food taken directly into the upper gastrointestinal tract will be utilized with maximum efficiency. If the patient can be induced to eat enough of the right type of food it is the best means of satisfying his nutritional needs. Unfortunately the very patients with the most severe nutritional disturbances are those usually incapable of tolerating a sufficient oral intake because of severe anorexia, vomiting, or organic obstruction.

The construction of a jejunostomy is a simple surgical procedure.² Jejunostomy feedings have the advantage of direct absorption from the intestinal tract and are less annoying to the patient than gavage feedings through a tube maintained in the nasopharynx for a number of days. Although the advantages of jejunostomies for feeding have been strongly supported by some surgeons,^{3,4} why have most surgeons so generally avoided them?⁵ This hesitancy to use jejunostomies has been due to two principal difficulties encountered in their actual use: first the formulas usually recommended although nutritionally excellent tend to produce abdominal cramps and diarrhea particularly in the first few days; second the formulas themselves contain many complex constituents and are difficult to prepare in the average hospital diet kitchen. Therefore in an effort to create a feeding which did not irritate the bowel and which would be simple to prepare a series of experiments have been conducted in the laboratory and on the hospital wards. After the clinical trial of many different mixtures the conclusion has been reached that commercial homogenized milk is the best basic constituent of a jejunostomy feeding.

The requirements for an ideal jejunostomy feeding mixture as set forth by Stewart⁶ were regarded as the goal to be attained. These requirements may be summarized as follows:

Read at the meeting of the Society of Laryngologists, San Francisco, Calif., March 1-26, 1942.

*National Institute of Health Research Fellow, U. S. Public Health Service.

†Aid by grant from Conely Fund, Ohio State University.

- 1 Adequate amounts of all nutritional elements
- 2 Inexpensive and easy to prepare
- 3 Easily digested and absorbed with low residue
- 4 Drips easily by gravity
- 5 Not too high salt or osmotic concentration
- 6 Relatively stable in refrigerator for 48 hours

The Scott's Emulsion⁹ has been widely advocated^{2, 4} because of its comprehensive nutritional composition. Nevertheless even in the experience of its advocates⁴ it tends to cause diarrhea and cramps requiring paregoric or its equivalent. The Hollander formula¹⁰ one of the best devised may produce diarrhea when first used if the quantity is sufficient to maintain nutrition even though jejunal tolerance may eventually develop. Although they are nutritionally complete the fact that there are thirteen constituents in the Scott's Emulsion⁹ and twelve in the Hollander formula¹⁰ renders it unlikely that they will be easily prepared by the average hospital kitchen staff. By way of contrast Allen¹¹ has found a simple mixture of equal parts of milk and lime water given in small quantities to be well tolerated by the jejunum even in the first few days but it is difficult to administer an adequate caloric content to maintain nutrition using this mixture alone.

The single food which most nearly seemed to meet Stewart's requirements⁵ for an ideal feeding mixture was whole milk. Milk is universally available of moderately high caloric value almost complete nutritionally and inexpensive. Recent investigators^{3, 10} have avoided the use of milk as a base for jejunostomy feedings because of the apparent intolerance of the jejunum to the fat in whole milk. In preliminary investigations an attempt was made gradually to increase jejunal tolerance to the fat in whole milk by starting the feeding with skim milk and adding increasing proportions of whole milk. The milk was peptonized to increase its digestibility.¹ Three out of the five patients on whom this system was used developed severe diarrhea and abdominal cramps by the time they were receiving whole milk. This seemed to be an adequate demonstration that it was impractical to introduce undiluted whole milk directly into the jejunum in sufficient amounts to maintain nutrition in the average patient.

Since it was assumed that the fat in the milk was producing the diarrhea attention was next turned to this aspect of the problem and to the theories of fat absorption mechanisms. The generally accepted lipolytic theory of fat absorption (Fig. 1) assumes that all fat ingested in the diet is completely hydrolyzed by pancreatic lipase to glycerol and fatty acids. The fatty acids are then supposed to conjugate with bile salts to form a water soluble fatty acid bile salt complex which is absorbed through the membrane of the cells of the intestinal mucosa. In these cells resynthesis is thought to occur to form phospholipids and triglycerides which pass both through the lymphatics and via the thoracic duct to the blood stream and through the portal vein to the liver. Collaborators from the Department of Physiological Chemistry assisted in determining whether the work of Frazer¹² dealing with fat absorption as related to particle size might be applicable to this problem.

LIPOLYTIC THEORY

PARTITION THEORY OF FRAZER

TRIGLYCERIDES OF DIET

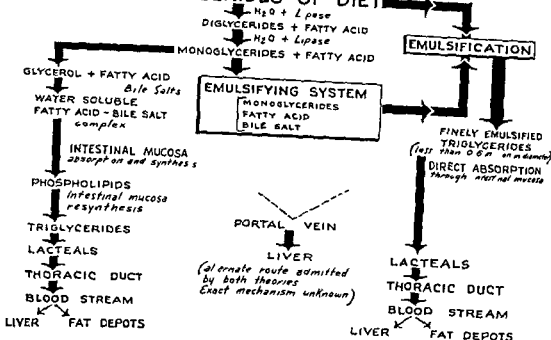


Fig 1—Theories of fat absorption. (All illustrations prepared by Mr Gabriel Ewaney medical illustrator Department of Surgery Ohio State University)




Fig —Size of fat globules in milk A Ordinary milk B homogenized milk Each of the small scale divisions represents 2 micra (Magnification X 90)

While Frazer did not deny the lyolytic theory in toto, he believed that in addition to this method of fat absorption by complete hydrolysis there is a second possible mechanism. (1) The monoglycerides and fatty acids produced by partial hydrolysis of some of the fat together with the bile salts present in the small intestine form an emulsifying system which acts with the remainder of the ingested neutral triglycerides to emulsify them into small neutral fat particles less than 0.5 micron in diameter, (2) these finely emulsified particles of neutral fat are then absorbed directly through the intestinal mucosal cells in unchanged form and pass either directly into the lacteals or into the blood stream leading to the liver. Frazer called this absorption of finely emulsified neutral fat particles *the partition theory of fat absorption*.

If the absorption of fat according to the partition theory does occur in the body it was postulated that perhaps the tolerance of the jejunum to milk fat could be increased by decreasing the particle size of the fat globules in milk. Fat particles in normal milk vary from 1 to 18 micra in size with an average of 4 micra while homogenized milk fat particles range from 0.5 to 2 micra in diameter with an average of 0.76 micra.¹⁴ This difference in particle size is well shown in Fig. 2.

HOMOGENIZED MILK

(PER LITER)

CONSTITUENTS	GRAMS	CALORIES
FAT (FINELY DIVIDED PARTICLES)	40	
CARBOHYDRATE	50	
PROTEIN	35	
		TOTAL 700 CALORIES

SUGGESTED DAILY TOTAL VOLUME

2400 cc { 84 GRAMS PROTEIN
TOTAL 1680 CALORIES

Fig. 2

The next step of the investigation was to try commercially prepared undiluted homogenized milk on dogs with Mann-Idollman jejunostomies¹⁷ and on patients with Stamm jejunostomies.¹⁸ In contrast to regular whole milk which had not been tolerated homogenized milk was tolerated regularly by both the dogs and the patients within twenty-four hours of the construction of the jejunostomy. In addition to possessing all the previously mentioned advantages of whole milk and also of having small fat particles homogenized milk provides per liter 700 calories and 25 Gm. of protein in a single solution (Fig. 3) while Scott and Ivy's pabulum¹⁹ with its thirteen constituents provides only 800 calories and 35 Gm. of protein per liter. *Vitamineral*²⁰

¹⁴ Synraf was kindly provided by its manufacturers, The United States Vitamin Corporation, New York.

¹⁷ *Vitamineral* 60 cc contains vitamin A, 5000 I. U. P. water, vitamin D, 1000 U. S. P. units, ascorbic acid, 10 mg, thiamin, 1 mg, riboflavin, 4 mg, pyridoxine, 1 mg, niacinamide, 4 mg, pantothenic acid, 2 mg.

LIPOLYTIC THEORY

PARTITION THEORY OF FRAZER

TRIGLYCERIDES OF DIET

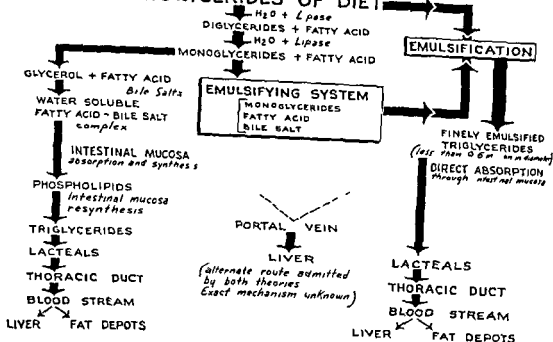


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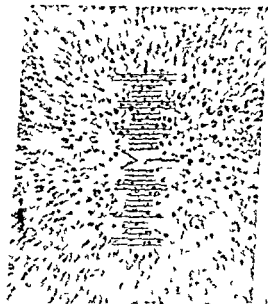



Fig —Size of fat globules in milk. A Ordinary milk. B Homogenized milk. Each of the small scale divisions represents micra (Magnification X9,000)

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²¹ Syneral was kindly provided by its manufacturers the United States Vitamin Corporation New York N. Y.





²² Syneral 86 cc contain Vitamin A 5000 I. U. S. P. unit, Vitamin D 1000 U. S. P. units, ascorbic acid 0 mg., thiamine, 1 mg., riboflavin 4 mg., pyridoxine 1 mg., niacinamide, 1 mg., pantothenic acid 1 mg.

(selected because it is water soluble and seems to mix the best with milk of the vitamin preparations tried) 0.6 cc is added to each liter of homogenized milk. This combination provides the standard vitamins in excess of the minimum daily requirements of each.

After many trials the following method of administration was developed and has proved to be well tolerated by a number of patients (Fig. 4).

1 Six hours after its construction, feedings of 5 per cent dextrose in normal saline solution are begun by gravity drip¹⁸ into the jejunostomy at a rate of 50 cc per hour. No ill effects have followed such an early utilization of the jejunostomy, which may be of theoretical value in preparing the jejunum for the more concentrated feedings to follow. Early distention of the jejunum likewise appears to stimulate intestinal motility, and may thereby lessen the number of adhesions.¹⁹

SHORT TERM JEJUNOSTOMY FEEDING PROGRAM (POST-OP MAINTENANCE)

POST-OP DAY	SUBSTANCE	METHOD	RATE	VOLUME	GRAMS OF PROTEIN	CALORIES
0	5% DEXTROSE IN NORMAL SALINE START 6 hrs POST-OP		50 cc / hr	VARIES	VARIES	VARIES
1	HOMOGENIZED MILK 0.6 cc VI SYNERAL / LITER		50 cc / hr	1200 cc	42	840
2	HOMOGENIZED MILK 0.6 cc VI SYNERAL / LITER		100 cc / hr	2400 cc	84	1680
3	HOMOGENIZED MILK 0.6 cc VI SYNERAL / LITER		200 cc / 2 hr with 50 cc of water	3000 cc	84	1680

CONTINUE THIS PROGRAM DAILY TILL ORAL INTAKE IS ADEQUATE TO ELIMINATE NEED FOR JEJUNOSTOMY FEEDING

*Supplement with IV fluids and Calories

Fig. 4

2 Starting at 7 A.M. on the day after operation (first postoperative day), homogenized milk is given into the jejunostomy tube by continuous gravity drip at the rate of 50 cc per hour providing 1200 cc of fluid and 840 calories in twenty-four hours. This may be supplemented if desired with 1000 to 2000 cc of 10 per cent dextrose in distilled water intravenously the last day that additional fluids are needed.

3 Starting at 7 a.m. on the second postoperative day the administration of homogenized milk is increased to 100 cc per hour by gravity drip. This provides 2400 cc of fluid 1680 calories and 84 Gm of protein daily which is more than adequate to meet the basic fluid caloric protein, mineral and vitamin requirements of the average convalescent patient.

4 On the third postoperative day the gravity drip may be discontinued. The homogenized milk is administered directly by aseptic syringe into the jejunostomy tube at the rate of 200 cc every two hours with 25 cc of water used before and 25 cc used after each feeding to wash out the tube and prevent clogging. The daily intake thus remains at 1680 calories and 84 Gm of protein but the fluid intake is increased to 3000 cc. For the succeeding days the same regime is followed.

Feedings must not be pushed too rapidly before normal bowel function is resumed. The patient must be observed for evidence of peristalsis or passage of flatus. If the lower colon does not empty within the first two or three days motility should be aided with an enema, rectal tube suppository or mineral oil given through the jejunostomy tube.

This regime starting with the day of operation and increasing gradually is outlined is designated the short term jejunostomy feeding program. Unsupplemented this simple regime with homogenized milk and Vit-Syneral will maintain a patient well for a five to ten day period. In the vast majority of patients oral feedings can be built up to adequate levels within this period after intestinal anastomoses or other radical surgery.

Certain patients however with severe malnutrition or inoperable total obstruction may require jejunostomy feedings for a protracted period. Further investigations were carried out to determine suitable mixtures with greater caloric and protein content for restoring and maintaining nutritional balance in such patients. The initial aim was to increase calories without proportionately raising the volume or changing the osmotic concentration and reaction of the mixture. The addition of fat could accomplish this because it is neutral and osmotically inactive.

Following the partition theory of Hazer it was decided to prepare finely emulsified fat mixtures of increased concentration. To aid in the emulsification recently developed non-ionic surface active agents known as Spans* (long chain fatty acid partial esters of hexitol anhydrides including sorbitins and sorbitides mannitins and mannides) and Tweens* (polyoxyalkylene derivatives of hexitol anhydride partial long chain fatty acid esters) were used. Spans and Tweens have been shown² to increase the utilization of orally ingested fat and to be tolerated by the small intestine in concentrations up to 1 per cent.³ The various Spans so thickened the milk mixtures by making a water in oil emulsion that they would not drip satisfactorily. The Tweens however aided in emulsification and stability of the final product. Tween 80 (polyoxyethylene sorbitin monooleate) used in 0.5 per cent concentration proved to be the most satisfactory for the emulsification of mixtures of milk

*Spans and Tweens are products of the Atlas Powder Company, Wilmington, Del. and were kindly provided by them.



and butterfat or corn oil and water. A one stage dairy homogenizer with 3,500 pounds pressure was used to break up the fat particles. Mixtures employing Tween 80 in 0.5 per cent concentration were passed through the homogenizer, resulting in emulsions whose fat particles averaged less than 1 micron in diameter as measured by a micrometer under a microscope. Of the particles, 95 per cent were less than 2 micra in diameter. Various concentrations of butterfat in milk (up to 12 per cent) and corn oil in water (1 p to 12 per cent) were thus treated and made available for feeding.

The dogs with Braun Bollman jejunostomies tolerated the 12 per cent fat mixtures of either milk and cream, or corn oil and water without diarrhea or discomfort. The patients with Stamm jejunostomies tolerated up to 8 per cent fat mixtures. Further investigations are being conducted to find the optimum fat concentration of milk and cream mixtures that will result in the best utilization of calories ingested by the body.

It was felt that the patients with severe nutritional deficiencies would profit by increasing the protein and carbohydrate components of the feeding mixture in addition to the fat component. It was observed that jejunostomy patients would tolerate a mixture of 10 per cent protein hydrolysate in water, or a mixture of 10 per cent starch hydrolysate in water. However, when either the 10 per cent protein hydrolysate mixture or the 10 per cent starch hydrolysate mixture was added to the previously tolerated 8 per cent emulsified homogenized fat in milk mixture the patients generally developed abdominal cramps and diarrhea. When all three components were mixed together and given, the patients always developed severe diarrhea, even if jejunostomy had been present for a considerable time. There was the further difficulty that in the preparation of the mixtures the added protein hydrolysate frequently broke the fat emulsions by its salting out effect and change in the pH. Only when the fat in milk emulsions were allowed to cool thoroughly before adding the protein hydrolysate or starch hydrolysate would the emulsions remain stable in the presence of added material. The difficulties encountered in preparing the high caloric mixtures and the tendency of the mixtures to produce diarrhea re-emphasized the fact that jejunostomy feedings must not have too high a concentration. The simpler they are the better they are.

After a series of experiments on dogs and patients employing varying concentrations of fat, protein hydrolysate and starch hydrolysate it was found that regular homogenized milk with only 4 per cent fat to which was added 50 Gm. of protein hydrolysate per liter and 60 Gm. of starch hydrolysate per liter produced the highest concentration that the jejunum would tolerate regularly. This mixture was called the "4-6 mixture" (4 per cent fat in milk, 5 per cent added protein hydrolysate, 6 per cent added starch hydrolysate). There are occasional patients who will not even tolerate this concentration, but the last seven patients have taken it well. To provide adequate amounts of iron and certain indefinite nutritional factors of whole liver, 50 Gm. of purified liver (pork liver as obtained in cans of baby food) are added to each liter of the mixture. This final mixture is called the long term jejunostomy feeding mixture and contains 1,151 calories per 1,100 cc. (Fig. 5)

LONG TERM JEJUNOSTOMY FEEDING MIXTURE (PER 1100 cc)

COMPONENTS	AMOUNT	CALORIES	
HOMOGENIZED MILK	1000 cc		
PROTEIN HYDROLYSATE	50 gms		
STARCH HYDROLYSATE	50 gms		
PUREED LIVER	50 gms		
VI SYNERAL	0.6 cc		
		FOOD COMPONENTS	NUTRITIONAL ELEMENTS
		TOTAL 1151 / 1100 cc	

SUGGESTED DAILY TOTAL VOLUME

2400 cc { 180 gms PROTEIN
2500 CALORIES

Fig 5


LONG TERM JEJUNOSTOMY FEEDING PROGRAM (NUTRITIONAL RESTORATION)

BEGIN AND BUILD UP FEEDING WITH HOMOGENIZED MILK AS IN SHORT TERM FEEDING PROGRAM FOR 5 to 9 DAYS TILL INTESTINAL FUNCTION IS NORMAL

THIS PROVIDES DAILY :

SUBSTANCE	METHOD	RATE	VOLUME	GRAMS OF PROTEIN	CALORIES
HOMOGENIZED MILK 0.6 cc VI-SYNERAL / LITER		200 cc / 2 HRS W N 30	3000 cc	84	1620

THEN FOR 2 DAYS

HOMOGENIZED MILK 0.6 cc VI SYNERAL / LITER		200 cc / 2 HRS W N 30	3000 cc	168	2100
50 GRAMS PROTOLYSATE / LITER					
50 GRAMS DEXIN / LITER					

IF WELL TOLERATED INCREASE TO FINAL MIXTURE .

HOMOGENIZED MILK 0.6 cc VI SYNERAL / LITER		200 cc / 2 HRS W N 50 OF W N 30	3000 cc	180	2500
50 GRAMS PROTOLYSATE / LITER					
50 GRAMS PUREED LIVER / LITER					

Fig 6

The long term jejunostomy feeding program for nutritional restoration of severe deficiencies over a long period of time is as follows (Fig. 6)

1 Homogenized milk is begun and gradually increased exactly as outlined previously in the short term feeding program. The patient is maintained on this regime for five to nine days.

2 When the patient is tolerating these feedings well with full return of normal intestinal motility and evacuation to each liter of homogenized milk is added 50 Gm of Protolysate* or of Protogest† and 30 Gm of Dexin‡ (a starch hydrolysate which contains 75 per cent dextrins and 25 per cent maltose). Added carbohydrate is preferred in the form of dextrins rather than simple sugars because of the smaller increase produced in total osmotic concentration.¹⁰ Protolysate or Protogest, 50 Gm provides 37.5 Gm of additional protein. The patient is fed 200 cc of this mixture every two hours by aseptic syringe directly into the jejunostomy tube with 25 cc of water before and after each feeding. This provides 3000 cc of fluid 2100 calories and 160 Gm of protein daily.

3 If the mixture outlined in the second step is well tolerated for two days the amount of Dexin is increased to 60 Gm per liter the Protolysate or Protogest is maintained at 50 Gm per liter and 50 Gm of purified liver are added per liter giving 1151 calories with 82.5 Gm of protein in each 1100 cc of the final mixture. This is fed at the same rate of 200 cc every two hours by aseptic syringe with 25 cc of water before and after each feeding to provide 3000 cc of fluid with over 2500 calories and 180 Gm of protein intake daily.

This long term jejunostomy feeding is more complicated, more difficult to prepare, and more prone to produce unwelcome symptoms than the simple short term feeding mixture. The long term mixture is to be reserved for the severely depleted patient only.

The Stamm type of jejunostomy has proved to be the simplest and best. Obstruction may occasionally follow the infolding carried out with the Witzel type jejunostomy, and hence has been abandoned in this clinic. The jejunostomy opening will close spontaneously with little drainage within forty-eight hours after removal of the tube.

SUMMARY AND CONCLUSIONS

1 Commercially prepared homogenized milk is a widely available economical, almost complete food substance. In contrast to whole milk it is well tolerated by the jejunum from the first day after construction of a jejunostomy probably due to the smaller size of the fat particles.

2 Sufficient amounts of homogenized milk can be given from the second day after construction of a jejunostomy to provide the basic fluid, calorie, protein, vitamin, and mineral requirements of the patient of average size.

*Protolysate brand of protein hydrolysate prepared and provided by Mead Johnson & Company, Evansville, Ind.

†Protogest brand of protein hydrolysate prepared and provided by Parroughs Wellcome & Co., Inc., New York, N. Y.

‡Dexin brand of starch hydrolysate prepared and provided by Parroughs Wellcome & Co., Inc., New York, N. Y.

THE INFLUENCE OF CALORIC INTAKE UPON THE FATE OF PARENTERAL NITROGEN

EDWIN H. ELLISON, M.D. ROBERT S. MCCLIFFRY, M.D. ROBERT M. ZOLLINGER, M.D., AND CLARKE T. CASE, M.D., COLUMBUS, OHIO

(From the Department of Surgery, Ohio State University College of Medicine)

THE widespread appreciation of the importance of nutrition, with particular reference to protein, has played a significant role in lowering morbidity and mortality in the surgery of poor risk patients. There is general agreement that the most effective method of nutritional therapy is by way of the gastrointestinal tract.^{1,2} In many instances, however, the only practical method of alimentation is by the intravenous route. As a result, there is increasing utilization of the various protein products which may be given intravenously.^{3,4}

The strong emphasis placed on meeting protein requirements has resulted in a tendency to overlook the importance of supplying a sufficient number of calories to meet basal energy requirements. If not met, the infused protein is burned as a source of energy and thus lost for tissue synthesis.⁵ Should the caloric deficit be very great, there may even be a ridding of tissue protein for energy needs.⁶ There has been considerable confusion as to what constitutes an optimal caloric intake. Figures varying from 6 to 45 calories per kilogram per day are to be found in the literature. The disagreement is more apparent than real and depends primarily on whether the desired end is protein maintenance or protein restoration (Fig. 1).

Florian^{7,8} has introduced the concept of "minimal" protein maintenance. "Minimal" defined as that caloric intake sufficient to prevent ketosis and tissue protein breakdown was found by him to be 6 calories per kilogram or 100 grams of glucose per day for the adult weighing an average of 70 kilograms. Experimental observations⁹ have suggested that the remaining energy requirement is supplied by catabolism of dispensable body fat. This applies only to normal individuals over short periods of time.

"Basal" maintenance implies protein conservation without expense to other body tissue. Putler and Talbot¹⁰ have recommended 25 calories per

1000 kcal requirement for parenteral maintenance and Levenson¹¹ Raydin¹²

pointed out that 30 to 45 calories per kilogram are necessary in order to realize any degree of protein restitution and weight gain. Dextrose solutions of 15 and even 20 per cent have been advocated to supply this energy requirement.

Nevertheless, one sees widespread use of 2 or 3 liters of protolysate containing 5 per cent dextrose per day with the belief that such a regimen will ensure nutritional restitution. It has been the purpose of the present study

Aided in part by a grant from the Mead Johnson & Company, Evansville, Ind.
Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March

to determine what constitutes the optimal caloric intake and by implication the concentration of glucose which ensures the most efficient utilization of parenteral protein supplied as a protein hydrolysate (Amigen®). The method employed has been carefully controlled nitrogen balance studies on human subjects.

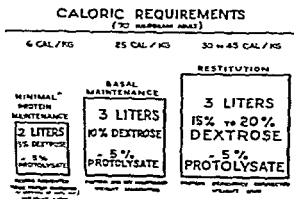


FIG. 1

GENERAL METHODS AND MATERIALS

A separate unit for metabolic studies was designed. This unit was staffed by special personnel whose only duties were those associated with the problem. These included a graduate dietitian, a laboratory technician, and special nurses over each twenty four hour period. All infusions were administered by a single member of the surgical staff so as to eliminate variations in technique. All foods were accurately measured and their nitrogen content calculated from standard reference tables and checked by sample analysis of the entire daily diet. Twenty four hour collections of urine, stools and other discharges were made and their nitrogen content determined. Samples of the parenteral solutions were analyzed for nitrogen. Stool collection periods were marked by enteric-coated capsules of indigo-carmin given on the first day of each period. Urine specimens were preserved by a single crystal of thymol. Food and stool specimens were preserved with concentrated sulfuric acid homogenized in a Waring Blendor diluted to 1000 cc and a sample taken for analysis. All specimens were refrigerated in closed containers from the time of collection until final analysis. The nitrogen content in each instance was determined by the standard macro-Kjeldahl procedure.

The twenty four hour urine specimens were tested for sugar qualitatively if sugar was present the exact amount was measured. Hematocrit levels total serum protein, and serum albumin and serum globulin values were determined at the beginning and end of each experiment. All laboratory analyses were made in duplicate.

The subjects were weighed daily under uniform conditions on a special scale. Local and systemic reactions to the intravenous solutions were carefully

*Applied by Warren M. Cox, Jr., Ph.D., Director of Department of Nutritional Research, Mead Johnson & Company

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"Basal" maintenance implies protein conservation without expense to other body tissue. Butler and Talbot¹² have recommended 25 calories per kilogram of body weight per day as the basal requirement for parenteral maintenance in adult individuals at rest in bed. Lund and Levenson¹³, Rardin¹⁴, Stare and Thorn¹⁵ and others¹² have repeatedly pointed out that 30 to 45 calories per kilogram are necessary in order to realize any degree of protein restitution and weight gain. Dextrose solutions of 15 and even 20 per cent have been advocated to supply this energy requirement.

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level of nitrogen nourishment to another always requires a varying period of adjustment. It follows that if the initial "bump" after supplementation is equal in all three experimental periods, the subsequent daily nitrogen balance and the average for each of the three day periods should be different if the higher caloric intake is accomplishing some degree of nitrogen saving. One can see by inspection that the initial degrees of nitrogen retention following supplementation are nearly identical. A study of subsequent daily balances and in particular, the average values (see Fig. III) for nitrogen retention during Periods I, II, and III clearly demonstrates an increased retention of protein nitrogen as the daily caloric intake was elevated by the use of 5, 10 and 15 per cent dextrose in Amigen. The effect was not cumulative as evidenced by the consistently negative balance of intervening depletion periods.

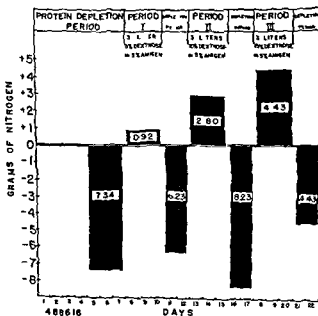


FIG. IV

The protein intake remained constant during the experimental periods at 113 grams per day, being supplied in each instance by 3 liters of 5 per cent Amigen. The one variable that of increased glucose concentrations or, in other words, increased caloric intake would seem to be the only explanation for the increased nitrogen retention. These findings agree with those of Cannon²⁷ who found in his work with dogs and rats that if adequate protein is assured tissue synthesis proceeds in a direct relation to the calories supplied.

In another representative patient (Case 2 Table II Fig. IV) handled in an identical manner to the first patient the relationship between caloric intake and nitrogen retention is even more strikingly demonstrated. A positive

TABLE I. INFLUENCE OF CALORIC INTAKE UPON NITROGEN BALANCE AT A HIGH LEVEL OF PARAPATHEL POTENTIAL ALIMENTATION
(CASE 1—M & 63 12 YRS OF AGE, CARCINOMA OF RECTO SIGMOID)

PERIOD	DAY	NITROGEN									
		INTAKE			ACCRETION			BALANCE			CALORIES PER DAY (PPH AC)
		GRAL (GM)	LI (GM)	WINE, STOOD (GM)	PPH DAY (GM)	PER PERIOD (GM)	PER PERIOD (GM)	PER PERIOD (GM)	PER PERIOD (GM)	PER PERIOD (GM)	
I 3000 cc 5% dextrose in 5% Amigen	1	11.0									2.9
	2	11.0									
	3	11.0									
	4	11.0									
	5	11.0									
	6	11.0									
	7	11.0									
II 3000 cc 10% dextrose in 5% Amigen	8	0	17.90	9.119	-6.099	-6.187					2.9
	9	0	16.900	9.078	-5.980	-6.187					
	10	0	17.140	9.025	-5.760	-6.187					
	11	11.0									
	12	11.20									
	13	0	14.710	9.612	-4.348	-6.187					
	14	0	14.810	13.344	-4.466	-6.187					
III 3000 cc 15% dextrose in 5% Amigen	15	0	15.040	14.997	-4.409	-6.187					2.9
	16	1.010	0	7.06	-6.83	-6.187					
	17	1.510	0	7.572	-6.060	-6.187					
	18	0	15.100	10.020	-4.498	-6.187					
	19	0	14.810	10.574	-4.426	-6.187					
	20	0	15.170	13.795	-4.345	-6.187					
	21	1.510	0	6.07	-5.92	-6.187					
Depletion	22	1.010	0	-1.110	-5.600	-5.601					2.9
	23	1.010	0	-1.110	-5.600	-5.601					

balance three times as great was obtained with 10 per cent concentrations of dextrose as compared with the 5 per cent and twice as great with the concentration of 15 per cent dextrose as compared with 10 per cent. Body weight increased steadily during supplementation. Supported by the fact that the hematocrit levels were the same or slightly higher at the completion of the experiment as compared to the base lines this weight gain probably represents tissue replacement rather than water retention. This coupled with the staircase effect on nitrogen retention, implies a more efficient utilization of protein at the higher levels of caloric intake.

PLAN OF STUDY

PERIOD	RAT	FEED NO.		PROGRAM		CALORIE PER KG	PROTEIN PER KG
		ORAL	NUTRITION	NUTRITION			
				VOLUME	SOLUTION		
DEPLETION	9	PROTEIN FREE DIET ADEQUATE CALORIES				40 KAL/KG	(GMS) 0
I	8	NO ORAL DIETARY INTAKE	2 LITERS	10 / DEXTROSE = 5 / AMIGEN		1170 23 CAL / KG	75
II	8	NO ORAL DIETARY INTAKE	3 LITERS	10 / DEXTROSE = 5 / AMIGEN		1155 35 CAL / KG	113

FIG V

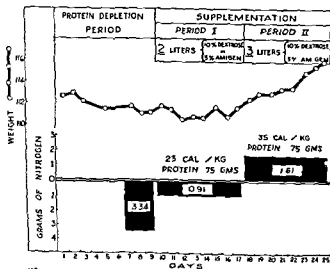


FIG VI

The usual precautions recommended for administration of hypertonic glucose solutions proved satisfactory. Local reactions were minimal, both as to degree and number. By maintaining the rates of infusion so that the ratio of glucose administration did not exceed 6 grams of glucose per kilogram

TABLE II. INFLUENCE OF CALORIC INTAKE ON NITROGEN BALANCE AT A HIGH LEVEL OF PARENTERAL PROTEIN ALIMENTATION
(CASE NO. 3, 4, 5 YEARS OF AGE, CAUSTIC CARCINOMA)

PERIOD	DAY	NITROGEN										FLUID	PARENTERAL GLUCOSE (GM.)	CALORIES PER DAY (PER AG.)	WEIGHT (POUNDS)
		INTAKE		EXCRETION	BALANCE		ACCUMULATIVE		FURTHER						
		OPAL (GM.)	LY (CM.)	URINE, STOOL (CM.)	PER DAY (GM.)	PER PERCENT (GT.)	LATIVE (GM.)	INITIAL (CC)	OUTPUT (CC)	ANCE (CC)					
I 3000 cc 5% dextrose in 5% Amigen	1	1.64		10.002	-9.42	-7.340	-22.0.2	3.300	2.7.0	730		34.1	118.1		
	2	1.68		9.4.0	-8.740			3.600	2.900	800	0	34.1	117		
	3	1.68		7.720	-6.040			3.900	3.200	900	0	34.1	116		
	4	1.64						4.000	3.500	500	0	34.1	115		
	5	1.68						4.700	2.730	930	0	21.6	113.1		
	6	1.64						4.4.0	2.6.0	1.630	0		114.1		
II 3000 cc 10% dextrose in 5% Amigen	7	0	18.6.0	14.4.0	-4.20	+9.20	+2.760	4.700	2.730	1.930	0		115		
	8	0	16.6.0	16.6.0	-3.9.0			4.700	2.730	1.970	0		116.1		
	9	0	16.6.0	18.9.0	-3.25			4.700	2.730	1.970	0		117		
	10	1.34	0	9.4.7	-0.17	-6.36	-12.437	4.700	2.730	1.970	0	33.4	118.1		
	11	1.34	0	6.7.0	-5.416			4.700	2.730	1.970	0		118.1		
	12	0	14.7.0	11.46.7	-3.281	+2.903	+8.419	4.700	2.730	1.970	0	32.5	117		
III 3000 cc 15% dextrose in 5% Amigen	13	0	15.100	10.1.8	-4.981			4.700	2.730	1.970	10.2		118		
	14	0	15.28	15.7.0	-0.043			3.900	2.540	1.360	16.7		119.1		
	15	1.8	0	10.38.7	-0.100	-9.296	-18.452	3.700	2.370	1.330	0	33.4	117.1		
	16	1.09	0	8.6.3	-7.343			3.500	2.200	1.300	0		117.1		
	17	0	15.007	9.1.3	-5.910	+4.409	+12.287	3.900	2.690	1.210	30.3	31.5	116.1		
	18	0	14.893	8.2.28	-6.657			4.700	2.730	1.970	45.0	31.5	115.1		
Deflection	19	0	14.917	13.2.97	-1.620			3.900	2.250	1.650	0	33.4	117.1		
	20	1.8	0	15.149	-0.269	-4.476	-8.900	3.400	2.270	1.130	0		117.1		
	21	1.28	0	30.964	-5.044			3.500	2.270	1.230	0	33.4	117.1		

Grateful acknowledgment is given to Warren M. Cox, Jr., Ph.D., Director, Department of Nutritional Research, Mead Johnson & Company for helpful suggestions and technical aid, also to Miss Margorie Brock, Department of Dietetics, Ohio State University College of Medicine for the preparation of diets used in the studies.

REFERENCES

- 1 Stewart J. D., Hale H. W. and Schaer S. M. Management of Protein Deficiency in Surgical Patients. *J. A. M. A.* 136: 1017, 1948.
- 2 Varco Richard L. Preoperative Dietary Management for Surgical Patients, *Surger* 19: 203, 1946.
- 3 Cox W. M., Jr. Nitrogen Retention on Casein Digests. *Proc. Soc. Exper. Biol. & Med.* 64: 197, 1949.
- 4 Elman R. Amino Acids in Regeneration of Serum Hemorrhage, *Proc. Soc. Exper. Biol. & Med.* 64: 197, 1949.
- 5 Kellum D. D., Hoffman W. S., and others. Nitrogen Retention on Casein Digests. *Proc. Soc. Exper. Biol. & Med.* 64: 197, 1949.
- 6
- 7
- 8 Brunchwig A., Clark D. E. and Corbin A. Postoperative Nitrogen Loss and Studies of Parenteral Nitrogen Nutrition by Means of a Casein Digest. *Ann. Surg.* 115: 1091, 1942.
- 9 Schwimmer D. and McGavack, Thomas H. Some Newer Aspects of Protein Metabolism. *New York State J. Med.* 48: 1797, 1948.
- 10 Elman Robert. Acute Starvation Following Operation or Injury With Special Ref. to Nitrogen Balance. *Ann. Surg.* 115: 1091, 1942.
- 11 Elman Robert. Nitrogen Retention on Casein Digests. *Proc. Soc. Exper. Biol. & Med.* 64: 197, 1949.
- 12 Bull J. H. Minimum Maintenance Requirements. *New England J. Med.* 231: 585, 1944.
- 13 Lund C. C. and Feven S. M. Protein in Surgery. *J. A. M. A.* 128: 95, 1945.
- 14 Pardin I. S. Nitrogen Balance. *Surger* 24: 1035, 1946.
- 15 Stare F. J. and Thorn W. C. Protein Nutrition in Problems of Medical Interest. *J. A. M. A.* 127: 1120, 1945.
- 16 Mueller A. J., Fickel D. and Cox Warren M., Jr. Minimum Maintenance Requirement of an Enzymic Casein Hydrolyzate, *Bull. Johns Hopkins Hosp.* 72: 110, 1943.
- 17 Cannon Paul R. The Utilization of Amino Acids in the Surgical Patient. *J. A. M. A.* 135: 1043, 1947.
- 18 Lockhart C. F. and Elman R. The Effect of Intravenous Glucose and Amino Acids on Glucosuria and Urinary Output in Human. *Surg. Gynec. & Obst.* 88: 97, 1949.

per hour, glycosuria and diuresis were avoided. This corroborates the recent work of Lockhart and Elman.¹⁹

It would seem therefore that with no greater effort on the part of the clinician or added discomfort to the patient, it is possible to double the efficiency of protein utilization without increasing protein intake.

Is it possible to arrange by simple calculations "basal" and "restitution" regimens for any given patient? Further balance studies were devised to answer this question.

The plan of study in one instance is shown in Fig. V. The observations represent complete metabolic studies of twenty-five days' duration. Stabilization was accomplished in a nine-day depletion period. This was followed by two eight-day periods of supplementation representing exclusive parenteral feeding for sixteen days. The 75 grams of protein and 23 calories per kilogram of Period I supplied by 2 liters of 10 per cent dextrose in 5 per cent Amigen corresponds to values accepted for maintenance. During period II the level of parenteral nourishment was increased to 113 grams of protein and 35 calories per kilogram which should result in some degree of restoration. The average nitrogen balance for each period is shown in Fig. VI. During Period I nitrogen equilibrium was not quite attained at calculated maintenance levels, however weight was maintained. On the other hand a positive balance was realized during Period II with corresponding weight gain. This again demonstrates that intravenous feedings may be useful even for long periods of time. As measured by the dual criteria of a positive nitrogen balance and weight gain a patient's nutritional status can be maintained and restitution assured provided sufficient protein and calories are given.

With one exception the *total serum protein* values were increased in all subjects. The exception, Case 2, actually represented a fall in a high serum globulin. The serum albumin was elevated in each instance.

In several cases in which these experiments preceded extensive abdominal surgery the patients underwent operation without difficulty and convalesced rapidly without complications.

CONCLUSIONS

1. The utilization of protein given intravenously is related to the total calories administered simultaneously.

2. Even though nitrogen intake remains constant nitrogen retention is increased when total calories are increased.

3. In practice the higher concentrations of glucose are preferable to the commonly employed 5 per cent glucose in 5 per cent protolysate.

4. The choice between 10 and 15 per cent concentrations of glucose and the total daily amounts of 5 per cent protolysate to be administered to any given patient will depend upon the goal of the clinician. For example an adult weighing an average of 70 kilograms will require 2 liters of 15 per cent dextrose or 3 liters of 10 per cent dextrose in 5 per cent protolysate per day for "basal" maintenance. The same patient will require 3 liters of 15 per cent dextrose in 5 per cent protolysate per day to assure restitution of protein and weight gain.

At the most past with the idea in mind of selecting a principle of repair which would nearly meet the requirements of providing an adequate repair in few operative steps in early childhood

HISTORICAL BACKGROUND

It is well recognized that hypospadias is an extremely difficult condition to correct. In an earlier report¹ we noted that the literature on hypospadias was voluminous and that the magnitude of the problem was attested to by the great number of procedures which have appeared in the literature. However we found after review of this mass of material that probably no more than seven different surgical principles had been reported in the past. We also discovered that the great majority of reports dealt with some minor modification of technique; reports dealing with an analysis of long term results are notable exceptions.

Since our earlier report reviewed in detail the principal types of repair previously reported they will be considered only briefly. The types of repair can be divided into two major groups. Flap repair and free graft repair.

Chronologically these are

1 Construction of urethra with flaps

- 1 Dieffenbach 1837-1845
- 2 Thiersch Duplay 1869-1874
- 3 Rochet 1899
- 4 Bucknall 1907
- 5 Ombredanne 1911

2 Construction of urethra with free graft

- 1 Nove-Jossier and 1897-1919
- 2 Miscellaneous methods, 1909-1927

Briefly these methods are

1 Construction of Urethra With Flaps—

1 Dieffenbach 1837-1845: The urethra was reconstructed by folding the ventral skin of the penile shaft into a skin lined tube which ended at the frenulum. This was covered over by undermining the skin laterally and suturing it in the midline over the skin tube. The two urethral lines coincided. If this was successful an attempt was made to draw the constructed urethral tube through the glans at a second operation.

2 Thiersch Duplay 1869-1874: This repair involved three surgical steps. First correction of the chordee by a transverse incision on the ventral half of the penis anterior to the meatal orifice. The first segment of the corpus spongiosum was excised. The skin was then closed after the principle of Heineke Mikulicz. Second the urethra was constructed from the ventral penis skin. This differed from Dieffenbach's procedure in that the incisions outlining the ventral skin to be turned upward to line the new urethra were made so that one ran parallel to and close to the midline and the other was made parallel and considerably lateral to the midline. When the skin was drawn over this turned in tube the two suture lines did not coincide. Third if the tube were successfully made the old and new urethra were joined.

PRI SCHOOL AGE REPAIR OF HYPOSPADIAS WITH TRIF IDIAL SKIN GRAFT

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ROCHESTER N Y

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HYPOSPADIAS is a congenital anomaly occurring when ventral closure of the urethral tube does not take place. The urinary meatus may be located from the perineum to the frenulum of the glans penis. In the more severe forms there is an associated ventral bowing of the organ called chordee. The curved, bent penis prevents normal sexual function and the abnormal position of the urinary meatus makes it necessary for the patient to sit down to urinate. Because of the abnormal appearance of the genitals psychic difficulties at times arise. These range from the troubles of the young boy twitted by his schoolmates because he cannot stand to urinate, to the morbid introspection of the adolescent regarding his deformed sexual apparatus, or to the actual later marital difficulties.

The objectives in correcting this condition are first an organ sufficiently straight on erection to allow satisfactory sexual function, second, a satisfactory urinary stream in the standing position, and third, near normal appearance.

It is commonly agreed that correction falls into two distinct procedures: the correction of the chordee and construction of the missing urethra. However, there is incomplete agreement on the type of operation which best accomplishes the desired result and the age at which the operation is best done. We do not wish to be dogmatic about these matters as have some who state that "but we do as urination e with a free

inlay skin graft

In general we believe that hypospadias has been repaired too late in life. The ideal time to repair congenital deformities is in early childhood and hypospadias is no exception. By so doing unnecessary mental anguish is avoided and the tendency of the deformity to become fixed is prevented. It seems probable that hypospadias repair is often delayed because of the greater ease in operating upon the larger organ of later years. This is particularly true of the various flap type repairs commonly used.

We began the type of repair presented here in 1940. We were dissatisfied with the results obtained by the usual types of chordee repair, the multiple operations necessary in the ordinary flap type of repairs for construction of the urethra, the late age often advised for urethral reconstruction, and the

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hole, and suturing the hole on the ventral surface of the penis. The urethra ends at the frenulum. At a second stage it is prolonged to the tip of the glans.

The chordee was corrected first. At a second stage in front of the abnormal opening of the urethra. A dull instrument was introduced through this opening and with it a subcutaneous tunnel made to the base of the glans. The anterior end of the tunnel thus made was perforated with a trocar. An Ollier-Thiersch graft was cut from the thigh. This graft was rolled on a No. 16 probe with its cutaneous surface inside. The clothed probe was introduced into the subcutaneous canal and kept in place by a convenient dressing. At the end of eight days the probe was withdrawn. Daily catheterizations were started to prevent contraction. This was kept up for about two months. The first patient operated upon was 18 years old. In 1914 Nové-Josseland reported the results obtained by this method in eighteen cases.

TABLE I. FINAL RESULTS REPORTED BY NOVÉ-JOSSELAND IN 1914

CASE NO.	TYPE OF HYPOSPADIAS	AGE (YR.)	RESULT
1	Penile scrotal		Good 1 year follow up
2	Penis		—
3	Perineal p. encephalohermaphrodite		—
4	Penile scrotal		—
5	Perineal		—
6	Penis	3½	Stricture
7	Scrotal	14	Good 7 year follow up
8	Penis	6	Good 2½ years
9	Penile scrotal	5	Good 6 years
10	Penile scrotal	7	Good 6 years
11	Scrotal	20	Good 6 years
12	Penile scrotal	13	Stricture
13	Penile	9	Good 5½ years
14	Penis	Adult	Fistula 4 years
15	Penis (juxtascrotal)	13½	Good 3 years
16	Penis	16	Stricture
17	Penile scrotal	34	Stricture
18	Perineal	7½	Good 18 months

2 Miscellaneous methods. Some tissues used for urethral reconstruction: saphenous or omentum vein, Leguen (1921); urethra Schmeelen (1909); appendix Weitz (1915); McGuire (1907); and Aschauer (1919); vaginal mucosa Leguen (1919).

RECENT PAPERS

Recent papers are concerned mainly with modifications of the procedures of Thiersch, Duplay, Bucknall, Ombredanne and Nové-Josseland.

Cecile and Lucknall and Thiersch Duplay procedures to repair hypospadias and fistula following Thiersch operation. Nahoum used a one-stage Thiersch Duplay procedure to correct chordee and mild hypospadias but the objection to this type of operation is that the future lines are directly superimposed and tend to fistula formation. Brendler leaves the glans widely open at the time the chordee is corrected in order to form an epithelialized trough. Subsequently the urethra is constructed by the Thiersch Duplay method.

Hansen combined the better features of the Thiersch Duplay and Ombredanne procedures. He is of the opinion that age is not a determining factor for undertaking this operation. Goodhope used a tube graft made from scrotal skin and suggested wire be used as suture material.

3 Pochet, 1899⁴⁰ The urethra was reconstructed with a flap taken from the scrotum with its base at the *hypopadias meatus*. In this way the temporary fistula between the old and new urethra was eliminated. (A step forward as the Dieffenbach and Thierch Duplay procedures both constructed the new urethra and later joined it to the old.) This flap was

The urethra ended at the frenulum
of ventral skin of the penis dorsally

on either side of the midline on the ventral surface of the penis. These were continued downward on either side of the median raphe of the scrotum. The *hypopadias meatus* was in the center of the rectangle thus outlined. The penile shaft was bent downward on the scrotum and the two flaps sutured together. A catheter was inserted through the newly constructed urethra. In three to four weeks the penis and the new urethra were dissected off the scrotum and the skin edges closed.

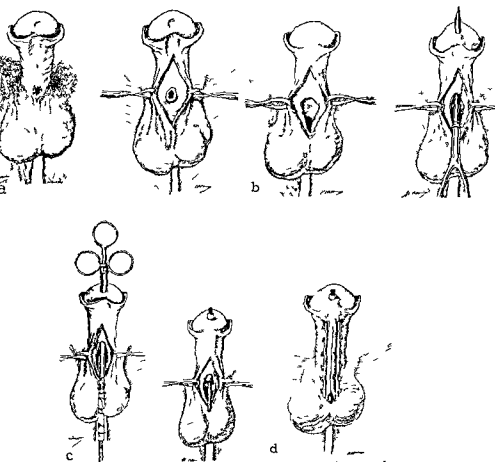


Fig 1—Reproduction of illustrations from Nové Josserrand

5 Ombrédanne, 1911⁴¹ The chordae is corrected at a separate operation. The urethra is made by an elliptical incision on the ventral surface with the *hypopadias meatus* in about its center. This flap is turned forward with a purse string around its periphery in the form of a pouch enclosing the *hypopadias meatus*. The raw surface left on the ventral surface of the penis is covered by buttonholing the preputial hood drawing the glans through the

spadias is of severe degree the scrotal portion of the urethra will contain hair. The meatus is at the frenulum. The urinary stream is often abnormal due to the patulous meatus and its abnormal location.

The Rocket principle is not good for the same reasons and, in addition, we felt certain that there would be circulatory difficulty at the distal end of a flap as long as needed with a necessarily narrow base.

The Bucknall operation's greatest objection is hair within the urethra. Otherwise it is probably foolproof. However as in the other procedures the meatus is abnormally located.

The Ombredanne operation is based on sound ideas. The main objection is that it is not suited to the more severe type of hypospadias. If after chordee correction the hypospadias is in the scrotum the urethra cannot be completely constructed by this method without reproducing some of the original flexion deformity. We feel that it is a good procedure for mild cases of hypospadias where there is little or no curvature and the meatus is near the frenulum. Even then the urethra is somewhat pouchlike and if a normal meatus at the tip of the glans is to be obtained a second operation is necessary.

Of all the procedures the principle of constructing the urethra with a free inlay skin graft as first advocated by Nove-Josserand appealed to us most. It appeared to have the following advantages. The urethra would probably not contain hair. Any length of urethral defect could be corrected. The urethra would end at its normal location in the glans. The likelihood of multiple fistulas forming seemed small since the urethra was formed in a subcutaneous tunnel. The appearance of the penis would be near normal and it might be possible to do the operation in quite young boys.

It is probable that reconstruction of the urethra by a free skin graft has never been widely used first because urologists who mainly attend these conditions were not familiar with the principles of skin grafting and second because as originally described the possibility of contracture of the constructed urethra was ever present. It is of interest that Nove-Josserand described free graft repair of hypospadias in 1897. The graft he used was an Ollier-Thiersch graft described and developed from 1872 to 1886 by Ollier and Thiersch.^{26, 27, 28} It is well known that the thin Thiersch graft has a high percentage of contracture. Despite this Nove-Josserand was able to obtain good results in nine out of eighteen cases which he reported in 1914.

The Nove-Josserand operation was revived in 1937 by McIndoe.^{29, 30, 31} He corrected the chordee when the patient was at the age of 2 years. This was done by the Edmunds procedure which necessitates two operations. At the first operation a tubed pedicle is prepared from the preputial hood. One month later the fibrous remnants of the corpora spongiosa are dissected out. The urethra is dropped back to its normal location and the ventral surface of the penis covered with the previously prepared preputial hood.

He then waited to construct the urethra until the patient reached the age of 7 or 8. This was done in the manner first described by Nove-Josserand using a thin razor graft. The subcutaneous tunnel was made with a trocar,

Smith and Blackfield¹¹ recommended the correction of the chordee at 18 months of age and then at a suitable time a reconstruction of the urethra by Thiersch Duplay flaps covered by crotal flaps (Blair operation¹²). The old and new urethra are joined at a second operation. In twenty patients they carried fourteen cases to completion seven of which were uncomplicated while in the remaining seven, one urinary fistula developed in each at the proximal end of the new urethra. Five of the six fistulas were closed at a third operation and two at a fourth. Thirty-seven operations were necessary to complete fourteen cases.

Kiefer utilized the Rochet principle of bringing a tube graft from the ventral penile surface out through the glans.

The Ombrédanne procedure has been used by Goldstein¹³ Muschat¹⁴ Barcat¹⁵ Loughran,²³ and others. Goldstein did not use a catheter in three patients, ages 30 months, 4 years, and 28 years with penoserotral hypospadias. Loughran presented the most critical review of a large series of cases over a long period of time. He studied fifty-nine cases of which forty-three could be traced. Twenty-nine cases were completed with twenty-four good results, but it is interesting that there were nine peno-, landular sixteen penile and only four scrotal types in this series.

Mummelair⁷ utilized the bladder mucosa as a free graft to form the urethra in a one-stage repair of hypospadias. He objected to the use of a skin graft because of the danger of infection and stated, "When bladder mucosa is used a real source of infection is omitted provided one is not dealing with some stage of cystitis. This seems like an unfounded statement to us. There are some objectionable features to this procedure, namely, (1) the skin along the penile shaft is laid wide open and (2) the suture lines are directly over each other. In both instances, we believe that fistula formation is quite likely to occur.

A most instructive paper in regard to differentiating male and female in an extreme deformity is that of Howard²¹. He found that, "In penile hypospadias, the urethra is normal. In penoserotral and perineal hypospadias, the urethra is markedly enlarged and may communicate with a well developed uterus.

DISCUSSION OF HISTORICAL PRINCIPLES

Chordee Correction—In reviewing these past procedures it seemed to us that the following criticisms were valid. The common operation for chordee is the so-called Hennenke Mikulicz in which a transverse incision is made just anterior to the hypospadias meatus. The fibrous cord is removed and the transverse incision closed longitudinally. This corrects the deformity to a certain degree. In severe deformities it is our experience that an adequate exposure of the entire shaft cannot be obtained. Some of the restraining fibrous tissue remains and the ventral skin cannot be satisfactorily lengthened. There is also moderate recontracture of the longitudinal incision. We have recorded a number of cases which had moderate bowing following this procedure.

The Edmunds^{14, 15} operation in which the preputial hood is shifted to the ventral surface of the penis is more satisfactory. It gives adequate exposure for a complete dissection of the chordee. There are two minor objections to it. The first is that it takes two stages at the first operation a preliminary ligation of the blood is done to insure blood supply. We have done this operation

safely done in one stage is preferable. The second objection is that the surface of the penis is somewhat objectionable. It tends to contract and the urethral reconstruction must be done under or in the flap operations around it.

Urethral Reconstruction—The Dieffenbach and Thiersch Duplay operations are prone to multiple fistulas forming along the suture line. If the hypo-

in the curved position. The urethra is freed by a circular incision and the dissection freeing it is done with a sound in place. When the proximal extent of the fibrous band is located, the urethra is retracted out of the way with stay sutures. An incision is made in the midline from the circular opening left by

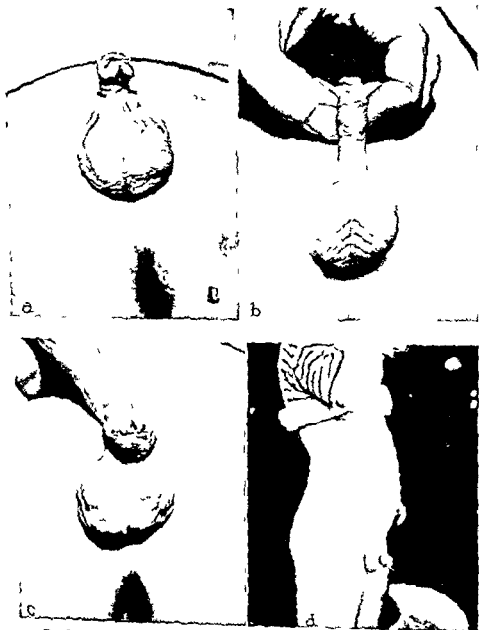


Fig. 2 (Case 9) — a Mild penile type of hydrospadias with usual chordae. b Chordae corrected, skin on ventral surface lax and urethral orifice well off midline. c Appearance of reconstructed urethra. d Five year old child voiding through reconstructed urethra.

and a catheter with a skin graft wrapped around it was introduced. A catheter was introduced into the bladder through the hypospadias meatus to prevent urine coming in contact with the graft. McIndoe said, "At the end of ten days the casing is removed. The gum elastic catheter is withdrawn and the skin lined urethra syringed through with saline or half strength encol. A permanent dilator of suitable size is then introduced into the new urethra and at no time is this left out for more than the five or ten minutes required to cleanse the canal. It is necessary to make this point absolutely clear to the patient and the parents for twenty four hours without the catheter will cause hopeless stenosis of the cavity in the early stages." After six months the dilator is left out and the epithelized canal is joined to the urethra after urinary diversion by external urethrostomy. Assuming that all steps go well this plan takes four operations and in our experience the joining of the urethra to the canal is not always successful.

Havens⁹ has advocated the McIndoe operation but insists that the urethra should not be constructed until the age of 16 years. We would agree that continuously wearing a dilator for six months would be impossible in a 2 or 3 year old boy perhaps difficult to accomplish in a child of even 7 or 8. The operation seems more applicable to adults or the late teens.

As we know skin grafts have greatly improved since Noël Tisserand's day so that more uniform grafts with less tendency to contract are now available. In addition the Foley indwelling catheter as well as chemotherapy and antibiotic methods of controlling infection have been devised. All of these factors caused us to believe that it was feasible to attempt to construct the urethra in one step even in small children.

OPERATIVE PROCEDURE

Correction of Chordee—As in all reconstructive procedures, a method gradually evolves and our experience is no exception. The steps reported are those we are now using. In brief we attempt to correct the chordee at one operation. This is done quite early if the patient is seen in infancy at about 1 year of age. In this respect most surgeons concerned with correction of chordee seem to agree. The advantages have been enumerated many times but for the sake of clarity they are: (1) The chordee should be completely corrected before the urethra is reconstructed. (2) Early correction of the deformity permits earlier urethral reconstruction. (3) Growth proceeds normally. (4) Deformities in general are most easily corrected before they become fixed by growth.

The objective of the first operation is to obtain a straight penis with lax skin on the ventral surface and if possible a plan which will prevent retraction to any extent. In addition we have found that it helps prevent fistula formation when the urethra is constructed if the urethral orifice is off the midline (Fig 2 b).

The first step is to dissect free the urethral opening. This dissection is carried proximally depending on the extent of the contracture. In any event one must be certain to excise all of the fibrous tissue which holds the penis

in the curved position. The urethra is freed by a circular incision and the dissection freeing it is done with a sound in place. When the proximal extent of the fibrous band is located the urethra is retracted out of the way with stay sutures. An incision is made in the midline from the circular opening left by

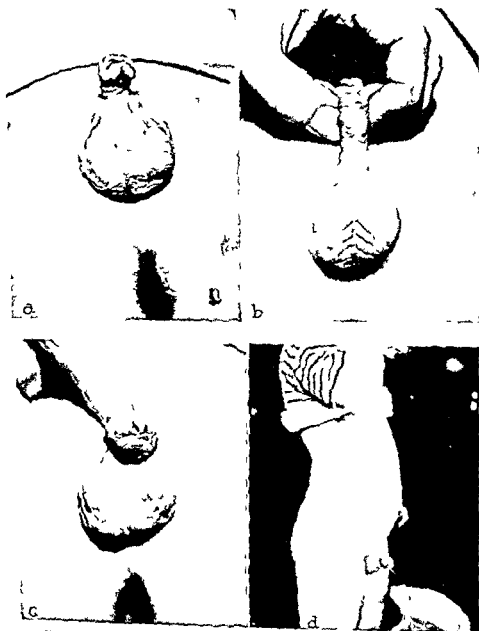


Fig. 2. (Case 9). —a. Mild penile type of hypospadias with usual chordae. b. Chordae corrected, skin in ventral surface lax and urethral orifice well off perineum. c. Skin inlay sutured in place. d. Five-year-old child voiding through reconstructed urethra.

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lateral wound to work through when later fashioning the urethra is sufficiently great to warrant this slight inconvenience

Sufficient skin for the added length of the ventral surface of the penis is usually obtained by the combination of wide lateral undermining cross cutting and triangular inserts and some shift from the hood which occurs from the correction of the deformed glans and the mucocutaneous incisions spreading laterally on either side of the frenulum (Fig 4, c) We have occasionally shifted the preputial hood by making a dorsal slit in the hood dissecting off and discarding the mucosal surface and rotating the halves of the hood skin to the ventral surface This should not be routinely done In a severely deformed penis with perineal hypospadias and vulviform scrotum we have on one occasion corrected the bifid scrotum at the same time the chordee was corrected by transplanting the two scrotal halves downward

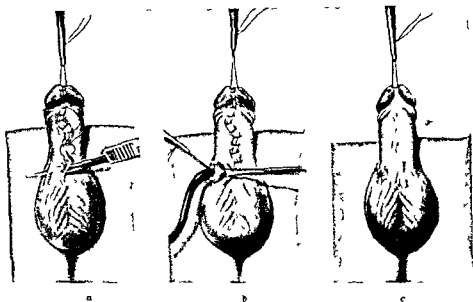


Fig 4—*a* The halves of the glans are brought together and the skin closed in multiple Z form to prevent later contracture. There is some shift of the hood ventrally to more nearly resemble the normal prepuce. A small tab wound is made laterally. *b* The free urethra is brought out the lateral stab wound and sutured to its edge. *c* The healed zig-zag scar with urethral orifice laterally.

After the skin has been closed the glans penis is sutured to the abdominal skin in extended position a Foley catheter is introduced through the urethral opening to the bladder to prevent urine flowing over the suture line and a compression dressing is applied over the penis to prevent edema and possible hematoma formation This dressing is left on for four or five days The catheter is removed when the wound is well healed usually in about seven days The suture is released from the abdominal wall a little later or when it breaks In all children it is imperative that the child be in bed with the extremities restrained We have not found that erections are particularly troublesome in either children or adults when a compression dressing is used and have not used any specific medication in an attempt to prevent them

freeing the urethra to the frenulum. At this point the incision branches to either side following the muco-cutaneous line. It then elliptically encloses the groove in the flattened glans. We did not originally do this but found that by so doing, the flattened glans could be made more presentable when the two sides were brought together and sutured (Fig 3, a)

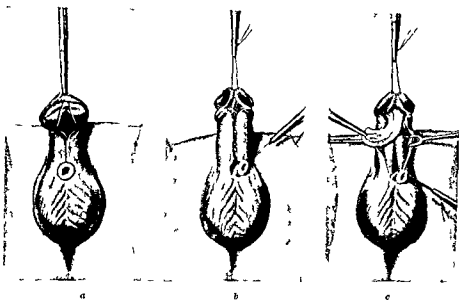


Fig 3—*a* The incisions for correction of chordee and flattened glans. *b* The urethra is dissected free the skin undermined laterally for complete exposure of the contracture and the sulcus in the glans excised. *c* Excision of fibrous tissue producing chordee the corpora are completely freed. Buck's fascia is cross cut or partially excised.

The skin on either side of the incision is freed thus exposing the contracted tissues. The fibrous band is dissected out beginning either proximally or distally as is expedient. The dissection of the band proceeds along the corpora cavernosa and must be quite close to it. In some instances Buck's fascia seems contracted and in order to secure complete straightening of the shaft must be crosscut or even partially excised. At this stage the corpora cavernosa are plainly seen. The urethral orifice has dropped backward and it should be possible to hyperextend the penis without any ventral tightness (Fig 3 c). Once the deformity has been corrected one must attempt to prevent postoperative scar contracture causing a partial return of the deformity. If the skin of the penis is closed longitudinally as in the Heineke Mikulicz principle this is almost certain to happen. To avoid this the closure is staggered in multiple fashion by imbrication of triangular flaps (Fig 4). We originally set the urethral opening off the midline by enclosing it in the most proximal of these zigzags but found that it could be more efficiently done by making a small stab wound through the skin well laterally and sewing the urethral end into this (Fig 4 a and b). There is a mild tendency for this circular wound to contract but a few passages of small sounds during the first one or two months is sufficient to overcome this. The importance of a

lateral wound to work through when later fashioning the urethra is sufficiently great to warrant this slight inconvenience

Sufficient skin for the added length of the ventral surface of the penis is usually obtained by the combination of wide lateral undermining cross cutting and triangular inserts and some shift from the hood which occurs from the correction of the deformed glans and the mucocutaneous incisions spreading laterally on either side of the frenulum (fig 4 c). We have occasionally shifted the preputial hood by making a dorsal slit in the hood dissecting off and discharging the mucosal surface, and rotating the halves of the hood skin to the ventral surface. This should not be routinely done. In a severely deformed penis with penileal hypospadias and uniform scrotum we have on one occasion corrected the bifid scrotum at the same time the cloride was corrected by transplanting the two scrotal halves downward.

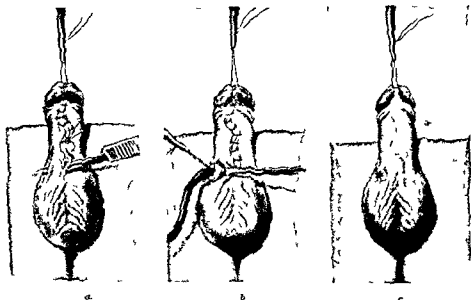


Fig 4—*a* The halves of Z form to prevent later contract resemble the normal 1/2 p. c. brought out the lateral tab near urethral orifice laterally

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Construction of Urethra—A varying period of time must be allowed to elapse for the tissues to soften thoroughly before the urethra is constructed. The minimum time is usually about six months. Before one begins the urethral construction, there must be minimal curvature of the penis, otherwise the organ will not be satisfactory sexually even though a urethra is present. The patient is followed at about monthly intervals noting any tendency of the penis to curve on erection and watching the state of the tissues to determine when urethral construction can be undertaken. If the child is around 1 year old when the chordee is corrected, we usually wait until he is about 2 or 3 years of age before making the urethra. This gives plenty of time for complete return of the tissues to normal and since the objective is to obtain normal urination before school age no time is lost. In adults the minimum time of six months may be a sufficient waiting period.

There has always been a difference of opinion as to whether or not to divert the urinary stream and the method to be used. We think it is only common sense to keep urine off the healing tissues, not so much because of infection but because of maceration. A perineal urethrostomy is simpler to do than a suprapubic cystostomy and with an indwelling Foley catheter is quite efficient.

The first step in urethral repair, therefore, is the urethrostomy performed high in the perineum. This site is chosen with the definite purpose of causing the urine to flow past the urethrostomy at more or less of a right angle rather than directly toward it, which occurs if the opening is lower where the urethra turns. We believe that this helps in prompt closure of the perineal urethrostomy after the catheter is removed (Fig 5).

The urethral orifice previously placed off the midline is encircled by an incision and is dissected free for about one half inch. This dissection is made well past the midline to allow the constructed urethra to return to the midline. A tunnel is made with scissors distally under the skin toward the glans. At the frenulum one must proceed carefully since the skin is thinner and more attached. The tunnel is carried through the glans emerging at the dimple where the normal meatus should be located (Fig 7). A skin graft about 0.020 inch thick is cut by the dermatome from the anteromedial aspect of the upper arm (Fig 6 a). This area is as nearly hairless as any obtainable. In 2 year olds this 0.020 inches may be greater than the thickness of the skin. The graft should be almost but not quite full thickness. After the first cut the dermatome should be reset if subcutaneous fat is seen. This graft is secured with dermatome cement to a catheter ranging in size from No. 14 to No. 18 French depending on the age of the individual and the size of the penis. At either end a No. 0000 chromic catgut tie encircles the graft and catheter to prevent rolling when the catheter and graft are introduced into the tunnel (Fig 6 b). Introduction is through the opening in the glans, the tip of the catheter being pulled on downward into the urethra. The catheter is turned so that the seam of the graft is dorsal. The tunnel should be of such size as to hold the graft covered catheter snugly. The tie around the introduced end of the graft

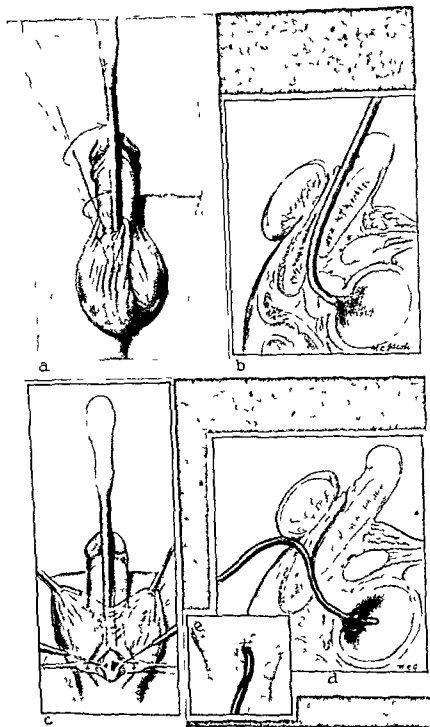


Fig 5.—a and b First step in urethral construction graft in place c Urethra opened rather high in perineum d Foley catheter in place e Wound closed snugly around catheter

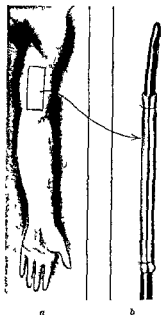


Fig 6—*a* Free graft cut with dermatome from hairless anteromedial surface of upper arm. *b* Graft fixed on catheter with dermatome cement. The two ligatures are to prevent rolling on introduction into tunnel. The tie at the end which is sutured to the urethra is removed after introduction. If the section of urethra to be constructed is short the preputial skin may be used for the graft.

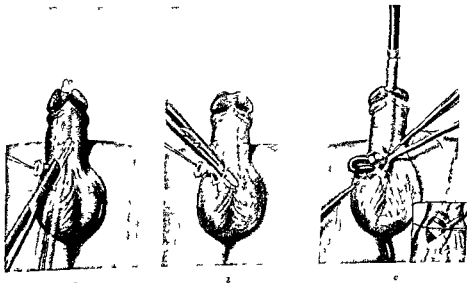


Fig 7—*a* under the skin and sutured medially. *b* introduced into catheter. *c* sutured into catheter.

is then removed since it has served its purpose. The graft and urethra are sutured with interrupted No. 0000 chromic catgut sutures onatraumatic needles (Fig 7 c). Since the urethral opening was off the midline the graft covered catheter comes to rest under a bridge of skin when dissected free. The closure of the opening is accomplished by suturing the deep tissues and then closing the skin with an end mattress sutures. This provides a folded surface for healing rather than edge to edge approximation. The object is to keep the suture line of urethra graft anastomosis and skin away from one another since this is the place where fistula formation is most common. The penis is elongated as much as possible by sliding it over the graft and a stitch transfixes the glans, catheter, graft and abdominal skin. Thus the penis is held in hyperextension (Fig 8).

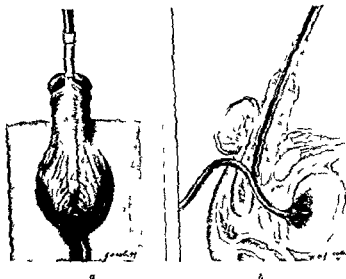


Fig 8—*a* Complete urethral reconstruction. The suture line of graft urethra anastomosis and of lateral wound do not coincide. *b* Sagittal section showing relationship of catheter, suture line and suture line.

The position on the abdomen facilitates the application of a compression dressing. Originally we immobilized the legs in an abducted position with plaster but we no longer do this as a simple compression dressing seems effective. This is applied with cotton voluminous gauze and elastic adhesive. In children the arms and legs are restrained. Originally we kept the graft bearing catheter in the penis for fourteen days and the perineal catheter for three or four days longer. As we gained more experience this time has been gradually decreased. We noted that at six or seven days there was often mucopurulent discharge at the penile meatus and similar discharge at the suture line on the shaft. Therefore we at present remove the catheter from the penis when it is no longer firmly adherent to the shaft and the indwelling perineal catheter on the same or next day. The patient is allowed to void in order to wash out the discharge. A catheter is then inserted through the penis into the bladder if the penile urethrostomy does not close in two or three days.

TABLE II ANALYSIS OF SIXTEEN CASES WITH IMMEDIATE AND LATE FINDINGS

CASE	HOSPITAL NUMBER (M.M.H.)	TYPE HYPSPADIAS	AGE CHORIOE CORRECTED	AGE LEFTURE RECONSTRUCTED	IMMEDIATE FINDINGS	FINAL RESULTS
1 J 9	14008	Circum	EL-EWHREE Complete Initially corrected	18 mo 3 yr	Small fistula	Fistula operatively closed at 4 yr Excellent at 10 yr
2 H 13	134 01	Scrotal	Complete Initially corrected	3 yr	Intact urethra	Excellent at 6 1/2 yr
3 J 6	14006	Scrotal	Complete Initially corrected	Chordee corrected and urethra con- structed in one stage 3 1/2 yr	Free suture necrosis from irrigating large fis- tula	Fistula operatively closed 9 mo later small sinus remained which closed, no follow up
4 G 1	9609	Scrotal	(complete) at 9 yr	10 yr (periputal graft)	Small fistula	Fistula operatively closed at 1 1/2 yr intact urethra good stream at 12 1/2 yr
5 J 16	1 16	Scrotal	Incomplete at 1 yr	12 yr	Intact urethra	Excellent 3 yr after repair
6 A 4	31 10	Scrotal	Incomplete at 4 yr	3 yr	Intact urethra	Excellent 1 1/2 yr after repair
7 D 3	58 57	Scrotal	Complete at 10 yr	11 yr	Small fistula	Urethra good through the glands, very tiny fistula 2 yr after re- pair
8 H 1	4 04	Circum		4 yr	Intact urethra	Perfect 1 yr later
9 W 6	103 15	Circum		8 yr	Small fistula	Fistula operatively closed at 9 1/2 yr, good, 1 1/2 drops in perineum on urination 1 1/2 yr
10 R 4	1088 4	Principal pseudo hernioplasty		1 yr	Small fistula at both urethral anastomo- sis and perineal urethro tomy	Two different attempts to close fistula second successful but patients gets ballooning of skin over fistula on urination Excellent 6 mo later
11 R 6	14 8	Penile	5 previous opera- tions for chordee and urethral con- struction chordee corrected	9 yr	Intact urethra	Fistula scars fully closed 1 yr later excellent 6 mo later
12 J 6	1214	Circumal pseudo hernioplasty		1 yr	Moderate fistula	Urethra scarred corrected fistula closed excellent 1 yr
13 R 10	43105	Penile		1 yr	Tiny fistula	Few drops from anastomotic site 6 mo after repair
14 L 6	31 18	Penile		3 yr	Tiny fistula	Few drops from anastomotic site 2 mo after repair
15 D 13	13304	Circumal	13 previous opera- tions for chordee and reconstruction of urethra	10 yr	Large fistula	Urethra operatively closed 1 yr after urethral con- struction result 1 yr 5 months no fistula

IMMEDIATE AND LATE RESULTS OF CHORDOE CORRECTION (TABLE II)

We begin this type of repair in 1940 nine years ago at the time of writing. In that period we have corrected twenty five chordoes. It has been necessary to reoperate in one case. In this instance there was partial slough of the tip of one triangular shifted from the hood. The scar healing caused some retraction but was mainly corrected secondarily because we did not think it would stand the tunneling and pressure necessary for urethral reconstruction. We rarely find it necessary to secure skin from the prepucial at the present time. The hood is drawn ventrally to a certain extent by correcting the ventral furrow in the glans and is transformed into an almost normal looking prepuce. From this series of twenty five cases it is evident that the plan as outlined for chordoe correction is completely satisfactory. In no instance has there been an appreciable return of curvature of the penis on erection. This can be easily determined even in a 2 or 3 year old by intentionally causing an erection during examination by handling of the organ.

TABLE III SUMMARY OF RESULTS OF CHORDOE CORRECTION

NUMBER OF CASES	RESULTS
4	
1	1
3	

RESULTS OF URETHRAL CONSTRUCTION

Immediate—In the sixteen patients in whom the urethra has been constructed at one operation five have had healing per primum with no leakage at any time and have voided through an adequate orifice in the glans penis as soon as the catheters were removed (Fig. 2). These we class as excellent immediate results. In the other eleven cases there has been some leak at the anastomosis of urethra and graft. This has varied from a sinus so small that it could not be seen without diligent search and allowing only a few drops to moisten the site on urination to a large obvious fistula allowing most of the urine to pass through. In all but four of these eleven cases the fistula has been quite tiny.

Late—The five immediate excellent results have remained so. Of the eleven others in three the fistula was tiny and so shrunk with time that only two or three drops of moisture were evident on urination. In these cases further surgery was not considered advisable. These patients could urinate standing without wetting the clothing and with a completely adequate stream. Of the eight remaining cases in five the sinus was completely closed by a second operation. In one case there were still a few drops even after the second operation for sinus closure but again as he could stand to void satisfactorily further surgery seemed questionable.

Thus out of sixteen cases eight have had satisfactory results in one operation and six in two operations.

Of the two remaining cases there is still about 25 per cent of the urine coming through an anastomotic fistula after two operations. A small fistula awaits closure at a third operation. This patient had been operated upon thirteen times previously in our own clinic, when he was from 2 to 16 years of age by the Thiersch Duplay technique with little success, the tissues were consequently quite scarred.

The remaining case is the only one we would class as a poor result. The patient was pseudohermaphroditic with a hernia and an undescended testicle on one side. The perineal urethrostomy had to be made far down in the perineum. It did not close and an anastomotic fistula also remained. Two different attempts were necessary before the two fistulas were closed. However, an internal fistula still remains since the skin balloons on urination and he has periodic bouts of periurethritis.

TABLE IV. SUMMARY OF RESULTS OF URETHRAL RECONSTRUCTION

NUMBER OF CASES	RESULTS
5	Perfect urinary function in one operation
0	Perfect urinary function in two operations (second operation to close anastomotic fistula)
3	Good urinary function in one operation (one to two drops of moisture at anastomosis on urination, further
1	

DISCUSSION

From these data it is evident that one can expect from these procedures a straight penis on erection in one operation. If the urethra is constructed in this way one can expect about one out of three patients to urinate normally after the initial operation and about 50 per cent to urinate satisfactorily.

It is worth noting that in no instance has there been a failure of the inlay graft taking. Furthermore fistula formation when it does occur is limited to the site of the urethral-graft anastomosis. If a fistula occurs it is not wise to attempt immediate closure although scarification of a tiny tract may occasionally be followed by complete healing. The fistula will spontaneously shrink and if the tissues are thick and the urethra somewhat removed complete healing may occur as long as three to four weeks after operation.

If an anastomotic fistula persists some months must elapse for the tissues to soften completely before an attempt is made at closure. If this is done over 50 per cent of the fistulas can be completely healed at the second operation. In the over all picture one can expect ten out of sixteen patients to urinate in a completely normal fashion and of the remaining six four will have satisfactory urination.

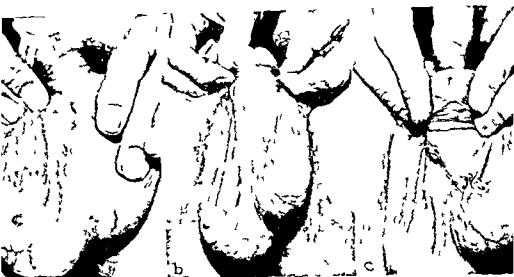


Fig 9 (Case 1)—a Condition in which patient first presented himself. Chordee had been satisfactorily corrected elsewhere. b Ventral view following urethral construction. c Retracted meatus in glans.



Fig 10 (Case 11)—a An extreme pseudomphroditic defect in which the penis is completely adherent on its ventral surface. b In the first five days after the urethral orifice retracts far posteriorly in the perineum when the penis is strangulated. c Final result, good urinary stream five days after urethral reconstruction.



Fig 9 (Case 1)—a Condition in which patient first presented himself. Chorley had been surgically corrected elsewhere. b Ventral view following urethral reconstruction. c Reconstructed meatus in glans.



Fig 10 (Case 1)—a An extreme pseudophimosis limits the penis to completely adherent on its ventral surface. b In this type of deformity the urethral orifice remains far posteriorly in the perineum. c In the penis is straightened. d Final result, good urinary stream 5 years after urethral reconstruction.

We believe that in the past the main reason for not using a free graft for urethral construction has been the fear of contraction and stricture. A follow up of our cases does not bear this out. At first we also had this lurking fear and dilated the constructed penile urethra frequently. We noted that this was often accompanied by bleeding and of course considerable discomfort. Because it seemed that the continual trauma would predispose to more scar tissue formation we abandoned frequent dilation and to our surprise found that the caliber of the stream in most instances improved. Evidently the urinary stream is sufficient in those instances where it passes through the urethra. If most of the urine comes through an anastomotic fistula more frequent observation and passing of sounds to determine whether dilation is necessary is advisable. The caliber of the stream is the best indication and on each follow up visit, the patient should be observed voiding if possible.

We have now observed two patients for nine years since construction of the urethra. Fortunately for our purpose one of these was a child 3 years old at the time of repair and the other an adult 39 years old. The child has maintained a completely satisfactory urinary stream and growth of the penis (Fig. 10). No tendency to stricture or for the chordee to return has been observed. This would seem to indicate that the graft has maintained a normal growth rate. The adult has developed no stricture and according to both him and his wife sexual function is normal (Fig. 9).

Both of these patients have been endoscoped. The graft in each instance bears a close resemblance to urethral mucosa. There was no hair present. At the site of the anastomosis a circular ridge was observed through which the instruments passed easily. It may be argued that the organ will become bowed as it becomes larger in adult life. Our opinion is that this will not occur. We know that skin grafts grow with the individual in other locations and presumably will here as well. We have watched our first patient grow from 3 to 12 years of age and there is no chordee on erection.

It has also been suggested that any tissue other than penile is not satisfactory for urethral construction because it does not have sufficient elasticity to stretch with erection. In Case 2 sexual function has been satisfactory for eight years. One patient (Case 6) married shortly after operation and had no difficulty. We believe constructing the urethra with the organ hyperextended and elongated and some stretching of both the old and new urethra by erections will contribute to satisfactory urethral length with the organ erect. This question will be finally answered when the 2 and 3 year old children are 18 and 20 years of age.

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1 The chordee deformity of hypospadias can be completely corrected in one operation when the patient is 1 year of age. This is accomplished by complete exposure of the corpora cavernosa, excision of the fibrous remnants of the corpus spongiosum, the furrow in the glans and often of part of Buck's fascia. The meatal orifice is transplanted laterally and backward, the halves of the glans and prepuce brought together, and the skin closed in zigzag fashion. In twenty-five cases there has been one reoperation.

2 The urethra can be reconstructed in a 2 or 3 year old patient in one operation. This is done with a free inlay skin graft.

3 The method makes multiple operations unlikely. In sixteen patients, ten have had a perfect result, four satisfactory, one poor, and one unfinished. Twenty-five operations have been done in these sixteen patients in constructing the urethra.

4 The advantages of this operation over the usual flap operations or the original Nove-Josserand or McIndoe's modification of it are many. The urethra has a normal exit in the glans penis; the urinary stream is therefore more normal and the appearance of the organ better than in penile flap operations. The urethra does not contract, as in most of the flap operations. Following flap operations it is not uncommon to have complete failure or multiple fistulas form. The poorest result in this regard when the urethra is constructed with a free graft is a fistula at the anastomosis of the graft and the urethra. The method avoids the two stages necessary in the Nove-Josserand operation and the risk of stricture or the prolonged wearing of a dilator as in the McIndoe operation.

5 We have had no case in which stricture has occurred and prolonged and frequent dilation of the urethra has not been necessary.

6 Finally, and most important of all, operation is applicable to pre-school age children and can be used for any degree of hypospadias.

REFERENCES

- 1 Buret J I. Traitement de l'hypospadias pénien et pénis crotal (Ombredanne procédé). J de chir 58 418 4^{me} 1942.
- 2 Blair V P, Brown J B and Hamm W C. The Correction of Scrotal Hypospadias and of Epispadias. Surg Gynec & Obst 57 646 653 1933.
- 3 Blair V P and Myers I F. Hypospadias and Epispadias. J Urol 40 814 825, 1938.
- 4 Brenner Herbert. A New Method for the Construction of a Clandular Urethra in Hypospadias. Repair. J Urol 59 1164 1168 1948.
- 5 Bucknall Rupert T H. A New Operation for Penile Hypospadias. Lancet 2 887 890 1940.
- 6 Cecil Arthur B. Repair of Hypospadias and Urethral Fistula. J Urol 56 237 242 1946.
- 7 Dieffenbach Johann F. Guérison des fentes congénitales de la verge. 1. De l'hypospadia (az méli le Par 6 156 157 1837.
- 8 Duplay Simon. De l'hypospadias pénis crotal et de son traitement chirurgical. Arch gen de mé 1 23 (V^e sér) 513 530 1874.
- 9 Duplay Simon. Nouvelle méthode opératoire pour le traitement de l'hypospadia. Arch gen de mé 1 23 (V^e sér) 513 530 1874.
- 10 Duplay Simon. Nouveau procédé opératoire pour le traitement de l'hypospadia. Arch gen de mé 1 23 (V^e sér) 513 530 1874.
- 11 Duplay Simon. Nouveau procédé opératoire pour le traitement de l'hypospadia. Arch gen de mé 1 23 (V^e sér) 513 530 1874.
- 12 Duplay Simon. Sur le traitement chirurgical de l'hypospadias. Bull et mem Soc chir 1^{re} sér 1^{re} 1874.
- 13 Duplay Simon. Sur le traitement chirurgical de l'hypospadias et l'epispadias. Arch gen de mé 1 23 (V^e sér) 513 530 1874.
- 14 Edmunds Arthur. J Urol 40 814 825, 1938.
- 15 Edmunds Arthur. J Urol 40 814 825, 1938.
- 16 Collie Albert F. J Urol 40 814 825, 1938.
- 17 Goodhope C D. Correction of Chordee and Hypospadias. Northwest Med 44 356 358, 1941.

A METHOD FOR CONTROLLING URINARY INCONTINENCE

EXPERIMENTAL OBSERVATIONS

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MANY children with lumbosacral myelomeningocele have neurological disturbances in the lower extremities with accompanying urinary and fecal incontinence. The urinary incontinence is in some respects the most serious problem that confronts these patients. It prevents them from engaging in normal activities and the resulting urinary tract infection is a frequent cause of death. Some of these children who have relatively minor cord lesions with adequate function of the lower extremities are prevented from living a normal and useful life only because of urinary dribbling.

Attempts to train these children to acquire urinary control through the development of a reflex urinary bladder have not been encouraging. This failure is particularly discouraging in comparison with the excellent results obtained in treatment of urinary incontinence associated with traumatic lesions of the lower spinal cord.^{1,2} This difference may be more apparent than real since long range programs used for treating paraplegic patients at the Army and Veterans Administration Hospitals have not been equaled in civilian practice. However the anatomic lesion of the cord in myelomeningocele differs from that in traumatic transection of the cord and therefore the possibility that prolonged training can achieve a reflex bladder in children with congenital anomalies of the lower spine is questionable.

Traumatic lesions of the spinal cord usually destroy but a short segment and normal cord below the transection is capable of playing its role in the function of the reflex bladder. Myelomeningocele on the other hand are usually associated with disruption of cord structures over a long segment and there may be no anatomic possibility of a reflex type of bladder. At the present time attempts to produce reflex bladders in children with cord damage are being carried on but have so far proved unsuccessful.³

At the present time there is no satisfactory technique for the relief of urinary incontinence in these children. Transplantation of the ureters into the colon is not feasible for practically all of the patients have an associated incontinence of the anal sphincter. In this clinic attempts have been made to construct a bladder by utilizing the sigmoid colon in several patients. This procedure consisted of implanting the ureters into an isolated loop of sigmoid colon which in turn was drained through the abdominal wall. In some of these patients the isolated loop serves as a reservoir and by intermittent catheterization the patients remain dry. Other patients in this group constantly leak urine

¹ and at the meeting of the Society of University Surgeons San Francisco Calif
March 1 & 2 1949

- 18 Goodhope C D The Use of Wire in the Repair of Hypospadias I Urol 54 4:1 473 1945
- 19 Hand F R Three Stage Repair for Penoscrotal Hypospadias Report of a Case, J Urol 59 414 421, 1948
- 20 Havens Fred J Hypospadias (editorial) Surg Gynec & Obst 87 339 240 1948
- 21 How F
- 22 Kieft
- 23 King
- 24 McIr
- 25 McIndoe A H The Treatment of Hypospadias Am J Surg 38 (n.s.) 1 6 195 1937
- 26 McIndoe A H Deformities of the Male Urethra, Brit J Plastic Surg 1 9-41, 1948
- 27 McIndoe A H, et al. A One Stage Repair of Hypospadias, with the Ombrellanne Operation for Hypospadias, Brit J Plastic Surg 1 9-41, 1948
- 28 Nové Joserand Gabriel Traitement de l'hypospadie nouvelle methode Lyon med 85 198 200 1907
- 29 Nové Joserand Gabriel Soc Bull Soc de chir de Lyon 7 3-5, 1904, 8 343 1905
- 30 Nové Joserand Gabriel Hypospadias penoscrotal Lyon med 108 923 1907
- 31 Nové Joserand, Gabriel Traitement des formes graves de l'hypospadie et de l'epispadie par la tunellisation avec greffe, Arch gen de chir 3 331 348 1909
- 32 Nové Joserand, Gabriel Resultats éloignés de urethroplastie par la tunellisation et la greffe dermo-épidermique dans les formes graves de l'hypospadie et l'epispadie, J d'urolog 5 393 406 1914
- 33 Nové Joserand, Gabriel De l'hypospadie étendue par la tunellisation avec greffe, Arch gen de chir 3 331 348 1909
- 34 Nové Joserand, Gabriel De l'hypospadie étendue par la tunellisation avec greffe, Arch gen de chir 3 331 348 1909
- 35 Nové Joserand, Gabriel De l'hypospadie étendue par la tunellisation avec greffe, Arch gen de chir 3 331 348 1909
- 36 Nové Joserand, Gabriel De l'hypospadie étendue par la tunellisation avec greffe, Arch gen de chir 3 331 348 1909
- 37 Nové Joserand, Gabriel De l'hypospadie étendue par la tunellisation avec greffe, Arch gen de chir 3 331 348 1909
- 38 Nové Joserand, Gabriel De l'hypospadie étendue par la tunellisation avec greffe, Arch gen de chir 3 331 348 1909
- 39 Nové Joserand, Gabriel De l'hypospadie étendue par la tunellisation avec greffe, Arch gen de chir 3 331 348 1909
- 40 Nové Joserand, Gabriel De l'hypospadie étendue par la tunellisation avec greffe, Arch gen de chir 3 331 348 1909
- 41 Nové Joserand, Gabriel De l'hypospadie étendue par la tunellisation avec greffe, Arch gen de chir 3 331 348 1909
- 42 Nové Joserand, Gabriel De l'hypospadie étendue par la tunellisation avec greffe, Arch gen de chir 3 331 348 1909
- 43 Nové Joserand, Gabriel De l'hypospadie étendue par la tunellisation avec greffe, Arch gen de chir 3 331 348 1909
- 44 Thiersch Karl Ueber Hautverpflanzung Verhandl d deutsche Gesellschaft f Chir (10th conference) pp 17 19 1881
- 45 Young Forrester and Benjamin John A Repair of Hypospadias With Free Inlay Skin Graft, Surg Gynec & Obst 86 433 441 1948

period that it was most likely to retract beneath the skin. This difficulty was overcome by the use of a large flange on the exposed end of the valve housing.

Our routine was to insert the closed valve into the bladder and to secure it in place with two purse string sutures. A small amount of the abdominal wall was excised in order to permit closure of the structures around the valve housing without tension or pressure on the tissue. This technique minimized edema, tissue necrosis, and infection. Provided due care in closure of the wound was taken, prompt healing occurred. When the prosthesis was firmly healed in place, the urethra was ligated and divided. This was usually performed about the tenth postoperative day. After the second operation the valve was left open for two to four days. This prevented the accumulation of urine in the bladder under pressure which might result in the creation of a urinary fistula through the closed urethra. The valve was then closed and the bladder drained twice daily (Fig. 2).

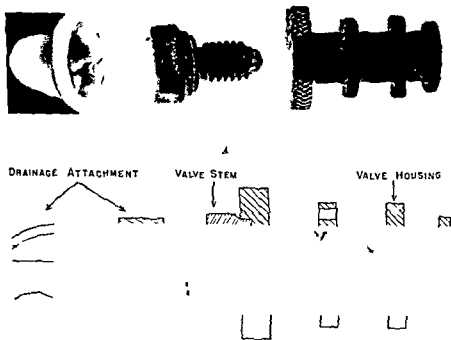


Fig. 2—A Exploded view of long bladder valve. B Construction details of bladder valve with drainage tube attached.

Bladder irrigations of various types were tried. All animals had solution irrigations at weekly intervals to prevent incrustations on the valve parts. Fortunately, the collection of urinary salts proved to be less troublesome than had been anticipated. Our longest period of observation was three months and incrustations on the valve were negligible during this time.

It was soon determined that bladder irrigations with such solutions as silver nitrate, Zephiran, streptomycin, and sulfadiazine encouraged rather

from the fistula despite intermittent drainage. Other methods of dealing with this problem have proved ineffective.

One solution would be the establishment of an external urinary fistula which could be controlled. Such a fistula would allow emptying of the bladder at intervals, and permit closure of the urethra thus preventing the dribbling of urine.

Studies were first undertaken to determine the ability of the abdominal wall and urinary bladder to tolerate a plastic tube. In nineteen dogs sections of polyethylene tubing, with solid flanged ends were inserted through the abdominal wall into the bladder.

In seven animals the tubes were too short and had inadequate flanges, consequently one end pulled out of the bladder and the other end retracted below the skin. In twelve dogs longer tubes carrying wider flanges were used. These tubes maintained their position. Observations covered periods as long as seven months. Leakage of urine did not occur and the tubes were tolerated with little reaction in the abdominal wall and bladder.

This experience encouraged us to insert a plastic valve mechanism into the bladder in a second group of dogs. Nylon now obtainable in rod form was selected as the most favorable material to use in the construction of a valve. Its tolerance by body tissue is established⁴ and its great tensile strength⁵, toughness and durability combined with its light weight made it the ideal material for our purpose. Furthermore this plastic can be autoclaved.⁶ Several designs were tried and finally it was demonstrated that a simple two piece manually operated valve was most dependable. This valve consisted of a housing, which was a tube with flanges at both ends. The outer flange was of greater diameter than the inner and was knurled to facilitate operation of the valve. The inside of the housing was threaded and a narrowed portion or valve seat was incorporated. The second part of the valve mechanism was the valve stem. This consisted of a threaded rod with a smooth rounded inner end and a knurled knob at its outer end. This rod was provided with holes which were so placed that when the valve stem was securely screwed into the valve housing a watertight seal was produced. One half turn in a counterclockwise direction disengaged the valve stem from the valve seat and permitted a free flow of fluid through the mechanism. The hole in the outer end of the valve stem was threaded to permit attachment of a drainage tube (Fig 1).*

Several problems were encountered in implanting the valve unit. In the first place to prevent rotation of the valve housing during the operation of opening and closing the valve projections were made on the housing around which the tissue could become firmly attached. The second and most trouble some problem was to prevent retraction of the prosthesis below the skin. Swelling of the abdominal wall usually occurred during the first few post operative days after insertion of the valve mechanism and it was during this

*This valve mechanism was developed with the help of Mr. Carl Henson and was manufactured by the Brunswick Manufacturing Co. Boston, Mass.

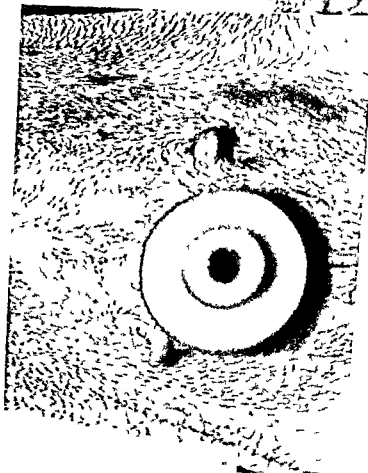
than prevented urinary infection. Our best results were obtained when no irrigations were performed. This may be explained by the impossibility of keeping a protective covering over the end of the valve. The animals invariably removed the rubber protecting cap which exposed the inside of the valve to contamination. It was impossible to clean the valve end so that when the irrigating tube was secured in place unsterile material was probably forced into the bladder. The bladder remained free of infection when frequent irrigations were discontinued.

Bladder valves were inserted into twenty dogs. Two of the animals died as the result of anesthesia. Four animals developed perivesical abscesses following urethral division and were sacrificed. Small urinary fistulas occurred in two animals, one beside the valve and the second through the wound. In the first animal the end of the valve became plugged with mucosa as a result of improper insertion into the bladder. Bladder drainage was established through a wound fistula. In the other animal the fistula was secondary to infection around the valve housing. Overwhelming cystitis with severe bladder spasm occurred in two animals and proved lethal in both instances.

Ten dogs did well and have been followed for periods up to three months. Periodic urine examination usually revealed two to four white blood cells per high power field in the unspun specimens. Retrograde pyelograms at three months in one animal outlined a normal upper urinary tract. Intravenous pyelograms in another animal one month after division of the urethra were within normal limits. The animals seemed comfortable on a twice daily drainage schedule and remained in good health through the period of observation.

Autopsy demonstrated little gross tissue reaction to the valve. The abdominal wall fitted snugly around the valve housing and adhered firmly in the region of the projections. The tract around the nylon prosthesis was lined with cystitis mucosa which in most instances continued to the skin of the abdominal wall. This lining was continuous with the bladder mucosa by both gross and microscopic examination. In some areas of the tract the mucosa was thinned out while in others it was of normal thickness. Around the fistula there was little histologic evidence of an inflammatory reaction (Fig. 3). At necropsy gross examination of the bladders exhibited minimal evidence of inflammation with slight redness of the mucosa as the only consistent change. Microscopic sections taken through the bladder wall contained evidence of mild submucosal edema and congestion. Small areas of round cell infiltration were occasionally observed. The mucosa remained intact throughout the bladder even in areas adjacent to the valve (Fig. 4). Gross examination of the ureters and kidneys revealed no evidence of ascending infection nor was dilatation of ureters or renal pelvis noted. Microscopic examination of the upper urinary tract showed no abnormalities. From the autopsy findings it may be said that the creation of artificial urinary fistulas by means of nylon tubes is followed by only minimal reaction in the urinary tract and that such prostheses are well tolerated by the bladder and by the abdominal wall.

Recently it has been determined that the urethra can be as satisfactorily closed by ligature as by ligature and division. This does away with the



A



B

Fig. —A and B views of bladder valve in place in the experimental animal. This valve was inserted one month before the photographs were taken



Fig 4—4 1 (mortem specimen of bladder six weeks following the implantation of a nylon valve unit. The valve tract was divided and may be seen at the bottom of the specimen. It is lined with a smooth layer of tissue which can be seen to be continuous with the bladder mucosa. The bladder is not dilated. The ureters are not dilated. II (X150) Section through the bladder wall. The mucosa is intact. There is slight edema but very little inflammatory reaction.

A



Fig. 3-4. Autopsy specimen with the valve tract left open. A. The valve has been removed and indented as made by the projections from the bladder mucosa. B. (X150) Sections through the tract at different levels. C. Note the transitional type of epithelium with which it is lined. On other sections this is seen to be continuous with the bladder mucosa. There is little inflammatory reaction.



Fig. 1—A. Post mortem specimen of bladder six weeks following the implantation of a nylon valve unit. The valve tract was divided and may be seen at each side of the specimen. It is lined with a smooth layer of tissue which can be seen to be continuous with the bladder mucosa. The bladder is shown in two parts in appearance. The ureters are not dilated. B. (X150) Section through the bladder wall. The mucosa is intact. There is slight edema but a very little inflammatory reaction.

source of infection which had resulted in the greatest percentage of failures in our experiments. An effective means of keeping the end of the valve sterile has been developed by using a close fitting finger cot filled with aqueous Zephiran 1:1000 to cover it. Since these refinements have been introduced no instance of severe bladder infection has been encountered.

SUMMARY

1. The need for effective control of urinary incontinence in children with myelomeningocele is discussed.

2. A method is described for the insertion of a nylon prosthesis (which includes a valve) into the bladder through the abdominal wall creating a urinary fistula which can be controlled.

3. Results of experiments on thirty-nine dogs are discussed.

4. Gross and microscopic examination of the urinary tract and the abdominal fistula demonstrate minimal inflammatory reaction to the valve housing.

5. This method for producing voluntary urinary control in laboratory animals has proved so encouraging that clinical trial of this procedure has been undertaken.

REFERENCES

1. Monroe D. Rehab.
Reference to
II Control of
2. Monroe D. Reha.
Special Refer.
Own Living
land J Med 236 2-3 23, 1944.

Nylon as Suture Material

kins Co
r 1944 School and College

7. Herger C C, Bauer H P, and Netter E. The Value of Stone Dissolving Agent Solution G (Citric Acid Solution) in the Treatment of Alkaline Incrustations of Bladder Lesion. Surg Gynec & Obst 77 634 638 1943.

THE ANATOMY OF THE NERVES SUPPLYING THE COMMON DUCT AND PROXIMAL DUODENUM

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THE detailed anatomy of the autonomic nerves in the region of the common bile duct and proximal duodenum has been investigated for many years. In a classic monograph published in 1834, Swan¹ fully described and illustrated the abdominal distribution of the vagus and sympathetic nerves. Subsequently, his work has been confirmed by numerous authors.²⁻⁵ Revival of interest in various types of nerve section for duodenal ulcer and biliary dyskinesia and in the laboratory investigation of these problems has stimulated workers to reassess themselves of the anatomic course and relations of the nerves supplying the stomach, duodenum, liver, biliary tract, and pancreas. This paper describes the anatomy of the autonomic nerves supplying the common bile duct and proximal duodenum, points out the importance of these structures in clinical and experimental studies and recommends a more exact nomenclature than is in general use today.

MATERIALS AND METHODS

Dissections were made of 15 recently sacrificed dogs and 20 human cadavers obtained both as autopsy and fixed specimens. Vagus nerves were traced from the neck to their abdominal endings and sympathetic trunks from the thorax to the celiac ganglia and likewise further along their abdominal distribution. Particular attention was given to all nerves directed toward the biliary tract and proximal duodenum.

RESULTS

Our studies have confirmed the reports of others. There is little difference between man and the dog in the abdominal distribution of the autonomic nerves and that difference is a quantitative one for the size and number of nerve trunks in man are much greater.⁶ Consequently the findings of both groups are analyzed jointly for simplification (Table I and Figs. 1 to 5).

LEFT VAGUS (ANTERIOR GASTRIC NERVE)

Immediately upon emergence from below the diaphragm one or more branches of the left vagus nerve extend toward the right and lying in the anterior layer of the gastrohepatic omentum, reach the porta hepatis. The major portion of these fibers usually the largest of the branches abruptly turns inferiorly along the common bile duct within the hepatoduodenal ligament and after giving off filaments en route reaches the proximal duodenum. The remainder of the left vagus fibers, those not directed toward the liver, then follow the lesser gastric curvature on its anterior surface and the largest becomes the principal anterior nerve of the lesser curvature of *Luttrell*.⁷

¹ *Ann. Surg.* 1834, 1: 1. At the meeting of the Society of University Surgeons, San Francisco, Calif., March 23, 1941.

TABLE I AUTONOMIC NERVES TO BILIARY TRACT AND PROXIMAL DUODENUM

UNMIXED VAGUS FIBERS	MIXED VAGUS AND SYMPATHETIC FIBERS
(1) Constant trunk from left vagus direct to porta hepatis and thence to duodenum	(1) From right celiac ganglion, filaments from right dorsal chain, greater and lesser splanchnics, and both vagi
(2) Inconstant trunk from right vagus to common duct region	(2) From left celiac ganglion, filaments supply this ganglion as on right (1), and join right celiac ganglion via celiac plexus
	(3) Mixed nerve fibers accompanying celiac axis via hepatic artery

Branches regularly supply anterior gastric wall from fundus to pylorus and also anastomose with right vagu fibers but do not pass into duodenum. Moderate sized filaments are distributed to the right celiac ganglion and smaller ones to the left. Others join the periarterial sympathetic trunks accompanying and branching with the celiac axis.

RIGHT VAGUS (POSTERIOR GASTRIC NERVE)

More often than not the right vagus nerve pierces the diaphragm as a single trunk. It immediately divides into several equal sized branches. One branch follows the lesser curvature of the stomach and is distributed to the posterior gastric wall in the same pattern as the left nerve anteriorly (principal posterior nerve of the lesser curvature).² There are connections or plexuses between the right and left nerves at the lesser curvature. Another branch from the main trunk, not constantly present, passes to the right through the posterior layer of the gastrohepatic omentum and supplies the common bile duct region. This trunk becomes unidentifiable in the nerve plexus around the common duct. Two other branches from the right vagus of large caliber occur constantly and run one to each side inferiorly and laterally, to fuse with the respective celiac ganglia. Some fibers are found along the celiac axis with the left nerve.

SYMPATHETIC NERVES

The sympathetic nerves are symmetrically arranged on the two sides and a description of one side only will be given. The dorsal chain and splanchnic trunks were followed from the chest to the level of the ipsilateral celiac ganglion. Whereas the dorsal chain usually sends a small branch to the ganglion, the greater and lesser splanchnics terminate in it, the greater merging with the upper portion and the lesser splanchnic with the lower or aorticorenal division of the ganglion. The least splanchnic is distributed to the renal plexus. The celiac ganglia, grossly similar to enlarged lymph nodes, are situated on the crura of the diaphragm at the level of the upper part of the first lumbar vertebra, one to either side of the midline near the adrenal glands. By means of the celiac plexus the ganglia communicate freely across the midline.

COMMON PATHWAYS OF VAGUS AND SYMPATHETIC NERVES LEADING TO THE BILIARY TRACT AND PROXIMAL DUODENUM

Both celiac ganglia receive a large number of vagus fibers preponderantly from the right vagus. There are abundant communications between the two



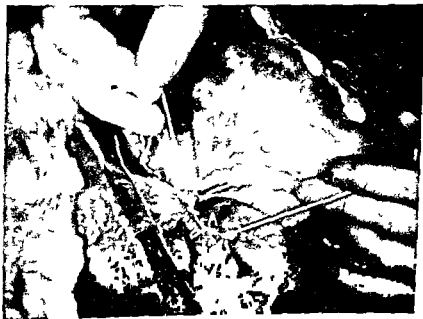
Fig. 1.—Dissection of right vagus nerve to show branches to celiac ganglia. The stomach and spleen have been rotated mesially and the diaphragm cut away. *A* Right vagus trunk from thorax. *B* Branches of vagus merging with periaortic sympathetics. *C* Left lumbar sympathetic chain. *D* Left celiac ganglion. *E* Branch from right vagus to left celiac ganglion. *F* Branch from right vagus to right celiac ganglion.



Fig. 2 (Dog 1st)—Dissection of right vagus nerve to show branches to celiac ganglia. The stomach and spleen have been rotated mesially and the diaphragm cut away. *A* Right vagus trunk from thorax. *B* Branches of vagus merging with periaortic sympathetics. *C* Left lumbar sympathetic chain. *D* Left celiac ganglion. *E* Branch from right vagus to left celiac ganglion. *F* Branch from right vagus to right celiac ganglion.



Fig. 3 (Case 9) —T

A Left
C Left

ganglia (celiac plexus). Emerging from the right celiac ganglion are several large nerve trunks which accompany the hepatic artery. These trunks are joined by vagus fibers traveling with periarterial sympathetics from the celiac artery region and are directed toward the common bile duct along the hepatic artery. As they approach this structure some filaments branch directly to the duct area and others anastomose to form a plexus. Within the hepatoduodenal ligament there are further anastomoses and branching not only with respect to the fibers from the celiac ganglion but also between these and the "pure" fibers direct from the left vagus.

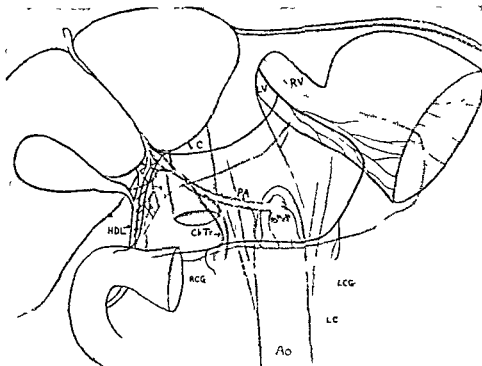
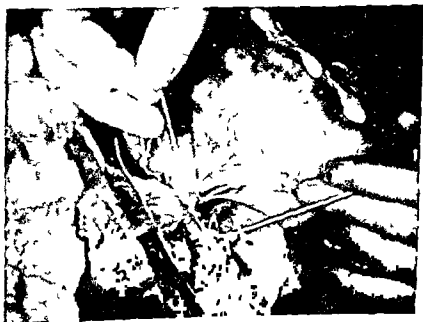


Fig. 1.—Diagrammatic sketch of the major pathways of the vagus and sympathetic systems in the upper abdomen. LC, left vagus.

In summary, the autonomic nerves supplying the biliary tract and proximal duodenum are as follows (Table I and Figs. 1 to 5).

1 *Unmixed Vagal Fibers*—The sources of these fibers are the constant branches of the left vagus to the porta hepatis and an inconstant one from the same nerve crossing directly through the anterior leaf of the gastrohepatic omentum to the lower portion of the biliary tract.

2 *Mixed Vagus and Sympathetic Fibers*—These make up by far the greater part of the autonomic nerve supply to this area. They arise from both



Experimentally, electrical stimulation or ablation of upper abdominal autonomic nerves has often been done to note the effect on function of abdominal viscera. Many of these experiments were carried out in the apparent belief that a "pure" sympathetic nerve group existed, whereas both vagus and sympathetic nerve elements were present.

Although the nomenclature describing the nerves in the gastrohepatic omentum and hepatoduodenal ligament should indicate their sympathetic and parasympathetic components, earlier authors and a few modern workers in this field have perpetuated terms which imply true anatomic and physiologic entities where none is known definitely to exist. Examples are 'nerf pancrea-choledochæen,'¹ 'gastroduodenal nerve,'² and 'nervus choledochi et pancreatici.'³ Since the majority of nerves in the hepatoduodenal ligament are composed of sympathetic and parasympathetic fibers and since the direct vagus branches anastomose freely with them, it is impossible to isolate a single nerve trunk that could be called a 'pure' nerve with the exception of the two vagus branches mentioned previously. For clarification it is recommended that the various combined branches to the biliary tract and proximal duodenum be called 'autonomic nerves' or 'mixed sympathetic and vagus nerves.'

SUMMARY

1 Dissections of the vagus and sympathetic nerves supplying the biliary tract and proximal duodenum have been done in 15 dogs and 20 human cadavers. The results confirm previous work of others and the following points are emphasized:

(a) With the exception of two branches coming directly from the vagi, the sympathetic and parasympathetic nerves follow common pathways in their course to the biliary tract and proximal duodenum.

(b) There is free anastomosis between the right and left-sided nerve trunks of both systems.

(c) Interruption of vagus nerve fibers must be done at the diaphragmatic level in the case of the sympathetics, the splanchnic celiac ganglia, and possibly the dorsal chains must be severed or ablated.

2 In operations for upper abdominal pain especially biliary dyskinesia the ineffectiveness of random sectioning of vagus nerve trunks in the subhepatic area is demonstrated.

3 Operations upon the sympathetic system in the upper abdomen both for clinical and experimental purposes are necessarily accompanied by interruption of some vagus fibers and the results should be so interpreted.

4 Recommendation is made to clarify the current nomenclature by replacing descriptive terms such as 'nervus choledochi et pancreatici' with other terms which denote their sympathetic and parasympathetic components such as 'autonomic nerves' or 'mixed sympathetic and vagus nerves' to the biliary tract and proximal duodenum.

REFERENCES

- 1 Swan J. *The Nerves of the Human Body*. London 1834.
- 2 Hellman. Quoted by McGee & Zisch. *J. w. anat. Zool.* 10: 417 1860.

celiac ganglia (the right and left ganglia are joined by the celiac plexus) and reach the common duct region along the hepatic artery and via the hepato duodenal ligament. The components of this mixture are chiefly filaments from the right vagus with a small number of left vagus fibers combined with large numbers of sympathetic fibers from the dorsal chains and greater and lesser splanchnic nerves and filaments direct from both vagi that merge with periarterial sympathetics along the celiac axis.

DISCUSSION

The exact pathways taken by vagus fibers after uniting with sympathetic trunks have remained an unsolved problem. In man it is assumed that since branches from both vagi enter both celiac ganglia the outflow from the ganglia is composed of both sympathetic and para-sympathetic fibers. By means of degeneration experiments this condition has been found by Alexander⁷ to exist in the cat. Since vagus fibers accompany the periarterial sympathetics of the celiac axis and its branches and also all the branches leaving the celiac ganglia and celiac plexus it is readily seen that the majority of the trunks in the gastroduodenal subhepatic region consists of a mixture of autonomic nerves. The vagus fibers proceeding directly to the biliary tract and duodenum represent a small proportion of total vagus fibers.

The clinical significance of the complex nerve pattern concerns surgical operations for upper abdominal pain, especially biliary dyskinesia. As in the past¹¹ surgeons have continued to section nerve trunks in the upper abdomen in the hope of relieving abdominal pain.^{8, 9, 11, 14} These operations have frequently been combined with celiac ganglionectomy or sympathectomy at higher levels. Since the sympathetics carry afferent pain fibers sympathectomy has been employed as a method for relief of abdominal pain of biliary tract origin.¹⁵ If the sympathectomy includes extirpation of one or both celiac ganglia as reported by Grimson¹⁴ then there is necessary interruption of many vagus fibers. This produces section of mixed nerves with dual function and it is difficult in analyzing the result to say whether pain relief was effected by the cutting of sympathetic or parasympathetic nerves. Regeneration of nerves after section in the hepatoduodenal ligament has been reported.¹² Splanchinectomy and celiac ganglionectomy must be done for complete sympathetic nerve interruption.

In operations designed to section vagus trunks in the gastrohepatic omentum as recently described by Jackson⁹ not only may sympathetic fibers be cut but only a small percentage of the total vagus fibers would be included in the designated area. The theory that overactive vagal impulses may cause postcholecystectomy pain an idea originally proposed by Oddi¹⁶ has been clinically tested by Crile,¹⁷ who obtained relief in two patients by subdiaphragmatic vagotomy. The success of this procedure is to be taken as clinical evidence of the role of the vagus in producing biliary tract pain in certain patients. It also points out the necessity of performing complete vagotomy at the diaphragmatic level rather than random sectioning of vagus branches at lower levels.

EFFECTS OF A NEW QUATERNARY AMINE AND A NEW IMIDAZOLINE DERIVATIVE ON THE AUTONOMIC NERVOUS SYSTEM

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NUMEROUS new drugs acting upon the sympathetic and parasympathetic divisions of the autonomic nervous system have been investigated during recent years. Some of these drugs block adrenergic neuro effector organ transmission others cholinergic neuro effector organ transmission and a few block cholinergic transmission occurring in autonomic ganglia. Examples of newer drugs blocking sympathetic nerve transmission at the effector organ are Priscol¹ I 933 a Benzodioxane derivative,^{2, 3} and Dibenzamine⁴. An ester of acetyl choline, Dibutoline⁵ has been used to block cholinergic pathways. The tetra ethylammonium ion according to Acheson and Moe⁶ prevents transmission of impulses through autonomic ganglia. Literature concerning actions of older drugs picrotoxin nicotine curine atropine ergotoxin yohimbine ergotamine tartrate F 883 etc have been described in a separate report⁷.

Two new compounds one a ganglionic blocking agent and the other an adrenolytic or sympatholytic drug have been investigated and are both reported in this paper similarities of effect upon functions of the autonomic nervous system are presented and differences contrasted.

The first of these new compounds is 2,6 dimethyl diethyl piperidinium bromide referred to in this report as SC 1950. It was demonstrated that it blocks transmission through autonomic ganglia in the experimental animal, this action being five to seven times as potent as that of tetraethylammonium chloride or Etamon. In unanesthetized dogs it reduced intestinal tone and contractility and in large doses (20 to 25 mg per kilogram) produced a flaccid curare like paralysis with respiratory death⁸. Our previous studies⁹ have in general confirmed this observation in animals and indicated similar effects in man.

The second of these drugs 2-(N p tolyl N (m' hydroxyphenyl) aminoethyl) imidazoline hydrochloride hereinafter called C 7337 has been shown by Meier and Yonkman⁷ to be a potent adrenolytic agent. Unlike Priscol however it had no cholinergic effects such as myotropic contractile activity in the experimental animal. This drug was effective by both parenteral and oral administration in animals.

*Support of SC 1950 and a grant in aid given by the Research Laboratories of G. D. Searle & Co. Chicago, Ill.

Support of C 7337 and a grant in aid given by Ciba Pharmaceutical Products, Inc., Summit, N. J.

Attest: In part by a grant from the American Foundation for High Blood Pressure held at the meeting of the Society of University Surgeons, San Francisco, Calif. March 1-6, 1949.

F. H. Longino, M.D., is a Research Fellow in Surgery.

Synthesized by the research laboratories of G. D. Searle, Inc.

- 3 Pernan Quoted by McCrea Arkiv f Zool Stockholm 10 p 11
 - 4 Latarjet, A Bonnet P, and Bonnot, A Les nerfs du foie et des voies biliaires
Lyon chir 17 13 1920
 - 5 Latarjet A Note preliminaire sur l'innervation et l'excitation de l'estomac Lyon
Med 130 106 1921
 - 6 McCrea E D The Abdominal Distribution of the Vagus, J Anat 59 15 1944
 - 7 Alexander, W F The Innervation of the Biliary System J Comp Neurol 72 557,
1940
 - 8 Franksson C The Innervation at the Common Bile Duct Duodenal Junction from a
Surgical Point of View Acta chir Scandinav 96 167 1947
 - 9 Jackson R C Anatomic Study of the Vagus Nerves, With a Technique of Trans
abdominal Selective Gastric Vagus Resection Arch Surg 57 303 1948
 - 10 McCrea E D The Nerves of the Stomach and Their Relation to Surgery Brit J
Surg 13 621 1946
 - 11 Jaboulay La chirurgie du sympathique abdominal et sacre (travaux de neurologie)
 - 12 Pearson Tabetic Gastric Crises,
 - 13 Lage Report of 10 Cases
in a Morphine Secretion
 - 14 Grim neural Results of Trans
Vagotomy or Trans
luminal Visceral Pain,
- SURGERY 22 200 1947
- 15 Adson A W Splanchic Pain Proc Staff Meet Mayo Clin 10 623 1935
 - 16 Oddi R D une disposition a sphincter speciale de l'ouverture du canal choledoque
Arch ital de biol 8 347 1887
 - 17 Crile G, Jr Subdiaphragmatic Vagotomy Incisions and Technic, Cleveland Clin
Quart 14 63 1944
 - 18 Johnson F F, and Royle E A The Effect of Sectioning Various Autonomic
Nerves Upon the Rate of Emptying of the Biliary Tract Surg Gynec & Obst
78 330 1944

LEI LOTS OF A NEW QUATERNARY AMINE AND A NEW IMIDAZOLINE DERIVATIVE ON THE AUTONOMIC NERVOUS SYSTEM

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(From the Department of Surgery, Duke University School of Medicine)

NUMEROUS new drugs acting upon the sympathetic and parasympathetic divisions of the autonomic nervous system have been investigated during recent years. Some of these drugs block adrenergic neuro effector organ transmission others cholinergic neuro effector organ transmission and a few block cholinergic transmission occurring in autonomic ganglia. Examples of newer drugs blocking sympathetic nerve transmission at the effector organ are Priscol¹ F 933 a Benzodioxane derivative^{2,3} and Dibenzamine⁴. An ester of acetylcholine, Dibutoline⁵ has been used to block cholinergic pathways. The tetraethylammonium ion according to Acheson and Moe⁶ prevents transmission of impulses through autonomic ganglia. Literature concerning actions of older drugs picrotoxin nicotine curare atropine ergotoxin yohimbine ergotamine tartrate¹ 883 etc. have been described in a separate report.

Two new compounds one a ganglionic blocking agent and the other an adrenolytic or sympatholytic drug have been investigated and are both reported in this paper. Similarities of effect upon functions of the autonomic nervous system are presented and differences contrasted.

The first of these new compounds is 2,6 dimethyl diethyl piperidinium bromide referred to in this report as SC 1930. It was demonstrated that it blocks transmission through autonomic ganglia in the experimental animal this action being five to seven times as potent as that of tetraethylammonium chloride or 11 amon. In anesthetized dogs it reduced intestinal tone and contractility and in large doses (20 to 25 mg. per kilogram) produced a flaccid curare like paralysis with respiratory death. Our previous studies⁷ have in general confirmed this observation in animals and indicated similar effects in man.

The second of these drugs 2-(N-p-tolyl)-N-(m'-hydroxyphenyl)-aminoethyl-imidazoline hydrochloride hereinafter called C 7337, has been shown by Miller and Yorkman⁸ to be a potent adrenolytic agent. Unlike Priscol however it had no cholinergic effects such as myotropic contractile activity in the experimental animal. This drug was effective by both parenteral and oral administration in animals.

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F. H. Longino, M.D., is a Public Health Research Fellow in Surgery
Sponsored in part by the Research Laboratories of G. D. Searle, Inc.

Experiments undertaken in this laboratory first evaluated the effects of SC 1950 and of C 7337 upon the circulatory system and gastrointestinal tract of dog and then extended to include trial and testing in man

ACTION OF SC 1950 AND C 7337 IN THE DOG

Method

Acute Experiments—Dogs weighing 9 to 16 kilograms were anesthetized using intravenous chloralose, 0.1 Gm per kilogram. A tracheal cannula was inserted, the carotid arteries isolated and the vagi divided. A left lumbar sympathectomy was performed transperitoneally. The right femoral artery was divided and cannulated proximally and distally; the left was also divided and then ligated proximally and cannulated distally. This permitted recording of three blood pressures using a mercury manometer connected to the proximal cannula in the right femoral artery to record mean systemic blood pressure and the two connected to the distal segments for measuring back pressure in the femoral arteries. Respirations were measured by a pneumograph connected to a recording tambour.

After preparation standard tests of the circulatory system were employed in each animal. Carotid sinus reflexes were elicited by occlusion of both common carotid arteries using bulldog clamps applied for one minute. Peripheral vagal stimulation was accomplished for 15 seconds using a tetanizing current from a Harvard inductorium set at 7 or 8 cm. Central vagal stimulation also employed a tetanizing current for 15 seconds but the setting of the inductorium was reduced to 6 or 7 cm. Epinephrine was injected as a 1:10,000 solution through a venous cannula. Neostigmine methylsulfate and pituitrin were also given intravenously.

These tests were each employed before use of one or the other of the two new drugs. SC 1950 was injected intravenously in doses of 0.5 to 20 mg. per kilogram or C 7337 in doses of 0.02 to 5.0 mg. per kilogram. The new drug employed for the acute experiment was administered several times to the same animal, often using larger amounts during subsequent injections. Tests were performed before and after the initial injection of the new drug and following each subsequent injection.

Experiments Employing Increased Intracranial Pressure—Dogs were anesthetized using chloralose, 0.1 Gm per kilogram; a tracheal cannula was inserted, blood pressure was recorded from a femoral artery and respirations were recorded. The two cervical vagus trunks were divided. A small area of the parietal bone was removed and a special manometer was inserted. The manometer was connected to the skull and the pressure was recorded at intervals during the observation period. If a rise in pressure and block of the carotid sinus reflex occurred, pressure within the skull was then increased by forcing saline solution through the trocar in the skull. Intracranial pressure was constantly kept above mean systolic blood pressure until death occurred.

Experiments in Unanesthetized Trained Dogs—Each new drug was given to trained unanesthetized dogs. Blood pressures were obtained before and at intervals during several hours following injection of the drug. Pulse rates were also counted. Each drug was tested using normal dogs and also using dogs made hypertensive three months to one year previously by bilateral excision of the carotid sinuses, division of one vagus trunk in the neck, and division of the depressor fibers of the other vagus trunk.

Each new drug was also given to trained, normal, unanesthetized animals after fasting 12 hours. A stomach tube was passed ten minutes after injection of drug and through it 30 Gm. of barium sulfate in 100 cc. aqueous suspension were administered. The tube was withdrawn and the gastrointestinal tract immediately observed fluoroscopically. Gastric activity was noted and the interval between administration of barium and initial emptying into the duodenum was accurately timed. Roentgenograms were obtained $\frac{1}{2}$ and 1 hour after administration of barium and subsequently at hourly intervals until 6 hours had elapsed.

Control Observations

Acute Experiments—Changes of blood pressure, pulse rate, respirations and back pressure in the divided femoral artery of a normally innervated and a sympathectomized hind limb occurring with occlusion of both carotid arteries, central or peripheral stimulation of one vagus, and injection of epinephrine, neostigmine or pituitrin are commonly known and details of several complete control experiments will be omitted. Rather results of the individual tests before administration of the new drug in each acute experiment will be referred later as effects of the drug are presented.

Experiments Employing Increased Intracranial Pressure—Increased intracranial pressure in normal dogs produced elevations of systemic blood pressure consistently over 200 mm. Hg and occasionally approaching 300 mm. Hg. Graded hemorrhage or histamine infusion sufficient to reduce blood pressure below 80 mm. Hg for $\frac{1}{2}$ to 1 hour variably reduced but did not prevent rise of systemic blood pressure with increased intracranial pressure.

Experiments in Unanesthetized Trained Dogs—Blood pressures and pulse rates of normal or neurogenic hypertensive dogs taken at hourly intervals fluctuated moderately. Spontaneous marked reduction of blood pressure was not observed.

Fluoroscopic examinations and subsequent roentgenograms in eleven animals revealed that normally or without drugs, gastric peristalsis was active. Emptying of barium into the duodenum began in from less than 1 minute to slightly less than 8 minutes. Average time of initial emptying was 4.1 minutes. Time required for emptying of barium from the stomach varied markedly in a few animals, but in most animals emptying times were similar. Average amount of emptying at $\frac{1}{2}$ hour was 30 per cent, at 1 hour 46 per cent, and at two hours 84 per cent. Gastric emptying was complete at 3 hours in eight of ten dogs. Of 9 dogs in which observations could be made with accuracy, the first of the barium had traveled through the ileum and reached the colon at 2 hours in three dogs and at 3 hours in six dogs.

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Observations Employing SC 1950

Acute Experiments—Acute experiments with SC 1950 were carried out in seven dogs using twenty three injections of the drug. Initial mean systolic blood pressure of the anesthetized prepared animals varied from 80 to 120 mm Hg. With three exceptions SC 1950 in dose ranges of 0.05 to 20 mg per kilogram consistently lowered blood pressure. With doses of 0.05 to 10 mg per kilogram, reduction of pressure was moderate lasting only 2 to 5 minutes. As dose increased, the depression of blood pressure became more pronounced and duration of depression lengthened. Doses of 5 to 20 mg per kilogram reduced blood pressure to one half or one third the level before injection and depression persisted 25 to 50 minutes. Small doses did not affect heart rate but 5 to 20 mg per kilogram produced cardiac slowing from an average rate of 159 per minute to an average of 93 per minute. This bradycardia persisted as long as did depression of blood pressure.

Doses of 0.02 to 10 mg per kilogram SC 1950 in three animals did not prevent vascular reflexes. In four animals receiving 5 to 20 mg per kilogram SC 1950 per injection, the rise of blood pressure normally occurring in response to occlusion of the carotid arteries was uniformly prevented in each of ten test periods. The rise of blood pressure occurring with faradic stimulation of the proximal divided vagus was prevented in three dogs and reduced in the fourth. Fall of blood pressure and cardiac slowing normally occurring with faradic stimulation of the distal divided vagus were blocked with one single exception following 5 to 20 mg per kilogram of SC 1950. In this exception blood pressure and pulse rate were reduced by peripheral vagal stimulation after 5 mg per kilogram but after an additional 10 mg per kilogram were not affected.

Blood pressure measured by cannulae in the distal ends of the divided femoral arteries representing back pressure or, indirectly, peripheral resistance, was lower in the sympathetomized extremity and responded slowly or passively in this limb during reflexes before the drug. Following SC 1950 peripheral or back pressure in the normal extremity decreased to equal that in the sympathetomized limb, and responses to cardiovascular reflexes were equally slow and passive.

Epinephrine two to four gamma per kilogram injected intravenously normally produced blood pressure increases ranging from 30 to 56 mm Hg following which blood pressure returned to pre injection levels in two minutes or less. After administration of 5 to 10 mg per kilogram of SC 1950 the response to epinephrine was enhanced pressures rising 46 to 168 mm Hg a response two to four times as great as that before SC 1950. The duration of the pressor response was increased to 3.5 to 7 minutes. The initial decrease of back pressure usually occurring in the normal leg following epinephrine was prevented by SC 1950 the response then being similar to that in the sympathetomized extremity.

In four instances 0.5 to 1.0 mg neostigmine methylsulfate was administered intravenously following SC 1950 in each case pressure rose to levels near those before SC 1950 and vascular reflexes again became active.

SC 1950 5 mg per kilogram was administered intravenously to seven dogs under ether anesthesia undergoing major abdominal surgery in the course of another research problem. Immediate cessation of respirations occurred in each of these animals. Three died of respiratory failure in spite of attempts at resuscitation. Four recovered after artificial respiration given for 3 to 5 minutes.

Experiments Employing Increased Intracranial Pressure—Doses of SC 1950 varying from 5 to 15 mg per kilogram intravenously were sufficient to prevent rise of blood pressure with carotid sinus reflexes and reduce blood pressure but did not prevent marked increase of systemic blood pressure in response to increased intracranial pressure in three dogs. It reduced this response partially in a fourth dog given 15 mg per kilogram intravenously. Increases of blood pressure during increase of intracranial pressure after SC 1950 were respectively 58 to 215, 100 to 280, 54 to 204 and 40 to 95.

Experiments in Unanesthetized Trained Dogs—Doses of 2 to 15 mg per kilogram of SC 1950 given normal unanesthetized dogs produced depressor responses in eleven of twelve animals average blood pressure before drug being 126 mm Hg and afterward 147 mm Hg. One dog had an immediate depressor response pressure falling from 126 mm Hg to 104 mm Hg and two others had an immediate rise of blood pressure followed by a fall to levels below normal. Pulse rates increased from an average of 88 per minute to an average of 142 per minute. In eleven tests on neurogenic hypertensive dogs there was a consistent lowering of blood pressure and slowing of pulse. Doses of 2 to 10 mg per kilogram SC 1950 lowered pressures from an average of 223 mm Hg to an average of 127 mm Hg with this reduction persisting 30 to 230 minutes. Pulse rates before the drug averaged 180 afterward 114.

Effect of SC 1950 on the gastrointestinal tracts of eleven normal trained dogs was studied. Doses of 0.4 to 10 mg per kilogram which are arbitrarily considered small caused rapid initial emptying thus usually occurring in one or two minutes. Similarly rate of emptying was increased as compared with normal dogs the stomach having passed 60 to 90 per cent of barium into the small intestine at $\frac{1}{2}$ hour in four of the five dogs and 90 to 100 per cent of barium within 1 or 2 hours. Barium reached the colon in two or three hours. Larger doses 5 to 10 mg per kilogram conversely effected marked delay of gastric emptying and of small intestine transit time. Initial emptying time averaged 29 minutes. The stomach had passed no barium in five dogs and only 20 per cent in the sixth at $\frac{1}{2}$ hour and required 3 to 6 hours to pass 80 per cent or more. Barium reached the colon only after 3 to 6 hours, transit time in the ileum being rapid as the drug effect wore off and gastric emptying occurred.

Observations Employing C 7337

Acute Experiments—Acute experiments with C 7337 were carried out on four dogs using thirty injections of drug. Initial mean systolic blood pressure of the anesthetized prepared animals ranged from 110 to 138 mm Hg. Intravenous injection of 0.02 to 0.05 mg per kilogram consistently produced decrease of systemic blood pressure. Duration of depression and degree of depression seemed directly proportional to amount of drug injected. With 0.02 to 0.05 mg per kilogram pressure was lowered slightly to 75 to 90 per cent of the level be

fore injection, and returned to pre injection levels after 5 to 8 minutes. With initial dose of 0.4 mg per kilogram or more, pressure fell to less than one half the pre injection level and remained depressed for as long as two hours. Following repeated injections in two dogs an initial slight rise of pressure (not over 10 mm Hg) preceded its depression, lasting 2 to 3 minutes in each instance. Pulse rate was increased by C 7337 in all dose ranges from an average of 171 before drug to an average of 204 after first injection.

Carotid sinus reflexes were active before drug in all dogs. Injection of 0.02 mg per kilogram reduced the pressor response to bilateral carotid occlusion and doses of 0.05 to 5 mg per kilogram either prevented this rise of pressure completely or markedly reduced the rise. Doses of 0.2 mg per kilogram or more reduced or prevented the pressor response normally occurring with faradic stimulation of the proximal end of the divided vagus in each thirteen tests. The fall of blood pressure and slowing of cardiac rate normally occurring in response to peripheral vagal stimulation was not affected by C 7337 in seventeen experiments.

The pressures measured in the distal ends of the divided femoral arteries were reduced by C 7337, and after the drug pressure in the normal leg approximately equaled that in the sympathectomized leg and responded more passively to vascular reflexes than before drug, thus resembling the sympathectomized extremity.

Following doses as small as 0.02 mg per kilogram C 7337, the pressor response to intravenous epinephrine 3 to 4 gamma per kilogram was markedly reduced. Following repeated injections of C 7337 or after injection of large doses there was a depressor response to injection of epinephrine. This effect was consistent in all experiments. A typical recording of an acute experiment illustrating adrenalin blockade is presented in Fig. 1.

Two animals were given 10 mg neostigmine methylsulfate following C 7337. There was no rise of pressure or other noted effect. In three cases surgical pilocarpine, 20 units intravenously, caused a rise of pressure with partial reactivation of vascular reflexes.

Experiments Employing Increased Intracranial Pressure—Doses of C 7337 varying from 2 to 10 mg per kilogram were sufficient to prevent rise of blood pressure with bilateral carotid occlusion and to reduce systemic blood pressure. They were also sufficient to decrease or prevent completely increase of systemic blood pressure during increased intracranial pressure in five dogs. A sixth dog tested after receiving only 2 mg per kilogram had a normal increase of blood pressure with this test pressure rising from 102 to 200 mm Hg. Pressures in the other five dogs changed during this test from 86 to 168, 58 to 95, and 74 to 100 in three deaths occurring in the remaining two with prompt decrease of blood pressure without preliminary rise.

A comparison of the effects of SG 1900 and C 7337 on the anesthetized dog is seen in Table 1.

Experiments in Unanesthetized Trained Dogs—C 7337 was administered orally, intravenously and intramuscularly to normal dogs in seventeen experiments and to dogs with neurogenic hypertension in twenty nine experiments.

Dosages used were from 0.5 to 2.0 mg per kilogram parenterally, and 2.0 and 5.0 mg per kilogram orally. Of seventeen tests in normotensive dogs receiving C 7337, thirteen had a reduction of pressure from an average of 126 mm Hg to an average of 101 mm Hg. Duration of depressor action in these dogs averaged 45 minutes after intravenous injection, 130 minutes following oral administration and 165 minutes when given intramuscularly. Twenty six of twenty nine tests in neurogenic hypertensive dogs showed reduction of pressure from an average of 199 mm Hg before drug to an average lowest pressure of 111 mm

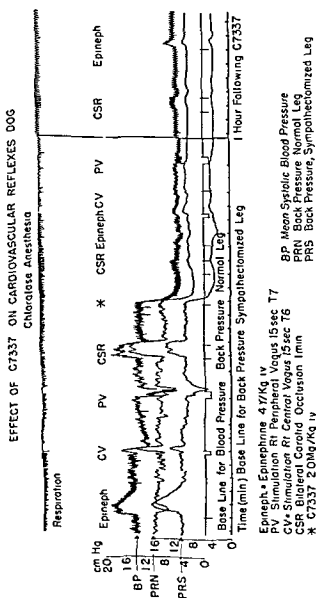


Fig. 1—A cassette record demonstrating effect of intravenous administration of C 7337 on standard cardiovascular reflexes of the dog. Chloralose anesthesia was used.

TABLE I A COMPARISON OF EFFECTS OF SC 1950 AND C 7337 IN DOGS ANESTHETIZED WITH CHLORALOSE

BOTH DRUGS		
	Lower blood pressure	
	Block carotid sinus reflexes	
	Block reflexes to central vagal stimulation	
	Wake reflex responses of back pressure in normal extremity like that in sympathectomized extremity	
SC 1950		C 7337
Blocks reflexes to stimulation of peripheral vagus		Does not block reflexes to stimulation of peripheral vagus
Slows pulse		Produces tachycardia
Accentuates action of epinephrine		Blocks pressor effect of epinephrine
Is reversed by neotigmine		Is not affected by neotigmine
Does not prevent hypertension occurring with increased intracranial pressure		In large doses prevents hypertension with increased intracranial pressure
Each dog received only one drug administered intravenously		

Hg afterward Average duration of the period of depression of pressure was 67 minutes following intravenous administration 148 following oral administration and 173 minutes following intramuscular injection Pulse rates were increased in eleven of the thirteen tests in normal dogs with reduction of pressure and in eighteen of the twenty six tests in hypertensive dogs having reduction of pressure after C 7337

Effect of C 7337 on the gastrointestinal tracts of six normal trained dogs was studied using 15 mg per kilogram intravenously Initial emptying of the stomach occurred in from 3 to 5 minutes in four, and was apparently delayed in two being 12 and 19 minutes All barium had passed from the stomach of one dog at 1 hour and of another at 2 hours Completion of emptying of the stomach of the other four dogs occurred in 3 to 6 hours as in the control animals In all six the first barium reached the colon in 2 to 3 hours as in dogs without medication

EFFECT OF SC 1950 AND C 7337 ON MAN

Sixty patients were given doses of SC 1950 varying from 0.5 to 2.0 mg per kilogram parenterally without ill effects Oral administration to six patients of 2 to 15 mg per kilogram (100 to 900 mg total dose) of SC 1950 produced only slight or inconsistent effects Forty one patients were given C 7337 intravenously and an additional thirty six patients received it orally Of these thirty received repeated oral doses every 2-3 or usually every 4 hours during treatment periods varying from 1 to 2 days to 4 months Dose ranges using C 7337 have been 0.5 to 2.0 mg per kilogram intravenously or orally since the drug has been as effective orally as parenterally Either drug was effective within a few minutes of intravenous injection Subjective symptoms following administration were similar — to a local feeling of warmth with some red dening of the was occasionally described Following intravenous injection there was an immediate marked increase of heart rate was noted which often annoyed the patient Within a few minutes of injection of SC 1950 dilatation of pupils, loss of accommodation and dryness

of the mucous membranes occurred. These effects did not occur following C 7337. Either drug occasionally caused ptosis of eyelids and engorgement of conjunctival blood vessels. C 7337 caused nasal congestion resembling that occurring after bilateral upper thoracic sympathectomy. These changes persisted for 30 to 60 minutes after intravenous injection of either drug. Intramuscular injection produced effects within 20 to 30 minutes which persisted 2 or 3 hours. Oral administration of C 7337 produced subjective changes in 30 to 40 minutes which persisted for 2 or 3 hours. After repeated oral doses symptoms became less noticeable and less objectionable. Urinalyses, red blood cell counts and differential white blood cell counts were performed on most patients tested and all treated several weeks or more. No significant abnormalities were noted.

Effects Upon the Cardiovascular System

SC 1950—With the exception of one patient who had slight pressor responses with repeated doses of SC 1950 lowering of blood pressure was consistently produced by 0.5 to 1.5 mg. per kilogram. The lowering of blood pressure readings obtained with the patient supine was more marked in hypertensive patients than in normotensives, average reduction being from 190/130 to 114/80 in the former and from 125/77 to 94/62 in the latter. Maximum fall occurred within 2 minutes of intravenous injection. Pressure then gradually rose to reach its former levels in 10 to 120 minutes. Duration of the depression varied according to the dose of the drug and also from patient to patient, but usually it persisted about $\frac{1}{2}$ hour. Reduction of blood pressure with standing was more pronounced and persisted for 1 hour or longer after return of supine pressures to control levels. Cardiac rate was not markedly affected but most patients had a slight tachycardia during the hypotensive effect of the drug.

Pressor responses normally occurring with immersion of hand in ice water for 60 seconds were tested before and after SC 1950 in fourteen patients. In each a pressor response was obtained before the drug. After 1.0 to 1.5 mg. per kilogram this pressor response to ice water was prevented or reversed in eleven cases, reduced in two and remained active in one. A pressor response was also obtained in each of sixteen patients before SC 1950 with prolonged breath holding in expiration. This response was prevented or reversed in twelve patients receiving 1.0 to 1.5 mg. per kilogram SC 1950 and reduced in the other four.

Six patients received 0.6 to 1.0 mg. of neostigmine methylsulfate intravenously during the hypotensive effect of SC 1950. Changes of blood pressure and pulse rate and block of pressor response to ice water and breath holding existing after the SC 1950 also persisted after the neostigmine methylsulfate. Time of return to normal after both drugs did not seem to differ from the expected time of return after SC 1950 alone.

Temperature gradients of lower extremities exposed at a constant room temperature of 21° C. were measured using a Cambridge thermocouple. Normal temperatures of the toes were several degrees lower than those of the umbilicus. This gradient was completely abolished, toes warming to equal temperature at the umbilicus, in nine of twelve patients receiving SC 1950 1.0 to 2.0

mg per kilogram intravenously. Two of the twelve patients had marked arterio-sclerotic occlusive vascular disease, in one there was no change of gradient and in the other the gradient was reduced. The remaining patient had a total dose of only 66 mg SC 1950 and had no change of gradient.

C 7337—Twelve hypertensive patients received 10 to 15 mg per kilogram of *C 7337* intravenously. Average blood pressure with patients supine before *C 7337* was 188/166. Afterward pressure was reduced in all twelve patients. Average lowest pressure following drug was 148/99. An additional patient had persistent hypertension following bilateral total thoracic and partial lumbar sympathectomy, splanchnicectomy, and coeliac ganglionectomy and had no reduction of pressure with *C 7337*. Eleven normotensive patients were given 10 to 15 mg per kilogram of *C 7337* intravenously. Eight had a fall of pressure from an average of 123/79 to 97/52. Blood pressure was not reduced in the remaining three. Effect on pulse rate was consistent, all patients having a more rapid rate after the drug. Average pulse rates of hypertensive and normal patients before the drug were, respectively, 78 and 81 and afterward were 112 and 129. With standing blood pressure decreased in all patients and there was a further increase of cardiac rate.

Pressor responses occurring with immersion of one hand in ice water were tested before and after *C 7337* in 11 patients, in 13 of whom pressor responses were obtained before drug. Following *C 7337* this response was prevented or markedly reduced in five patients, was somewhat diminished in two and occurred as before the drug in seven. A pressor response with prolonged breath holding was obtained in eight of fourteen patients before drug. Following *C 7337* in these eight patients the pressor response was prevented in one, decreased in two and occurred as before the drug in five.

Skin temperature gradients were measured in twenty seven patients. The normal gradient of the exposed lower extremities was completely abolished in eighteen of the twenty seven patients, toe temperature equaling temperature at the umbilicus and markedly reduced in two others. The block of temperature gradient produced lasted from 1 to 3 hours. Among the remaining seven patients one with severe Buerger's disease in the left leg had a block of gradient in the right leg but no change in the left. Five with advanced arteriosclerotic occlusive disease and one with severe Raynaud's disease had no warming of extremities or loss of gradient. Two of the arteriosclerotic patients with no change of gradient following *C 7337* had lumbar sympathectomies performed later and in neither was skin temperature gradient improved postoperatively.

Since many of the patients tested with *C 7337* had some form of vascular disease electrocardiograms were obtained in each before administration of drug. *C 7337* was not given to patients with a history suggestive of anginal type pain or with significant abnormalities in their electrocardiograms. Nevertheless, three patients receiving 10, 12 and 15 mg per kilogram respectively intravenously and having reduction of blood pressure experienced sub-ternal pain lasting 2 to 3 minutes. This pain was relieved by nasal oxygen. Subsequent electrocardiograms a few days later revealed no abnormalities.

Effects Upon the Gastrointestinal Tract

SC 1950—Gastrometric and intubation balloon studies of the small intestine were performed in 20 patients. Three hundred cubic centimeter balloons were used in the gastrometric studies of the fasting stomach. They were placed in the fundus and mid-stomach under fluoroscopic guidance and connected to a recording bromoform manometer. Twenty cubic centimeter balloons one on a Miller Abbot tube or 4 eight inches apart on a four lumen tube (Chapman, Stanbury and Jones¹¹), were employed to determine effects upon the motility of the small intestine.

Administration of 10 to 15 mg per kilogram of SC 1950 intravenously consistently caused decrease of resting intraluminal pressure or 'tone' and of forceful fluctuations of pressure of peristalsis in both the stomach and small intestine. Gastric tone began rising 25 to 40 minutes following SC 1950 and after 60 to 80 minutes was often slightly greater than before the drug (Fig 2). Peristaltic activity ceased in the stomach for 30 minutes or more in all cases, an average of 58 minutes elapsing before return of contraction waves. In the small intestine decrease of tone and absence of contraction waves persisted somewhat longer than in the stomach. In the small intestine normal contractions appeared within a few minutes of resumption of activity but gastric contractions were reduced for 30 minutes or more after their return.

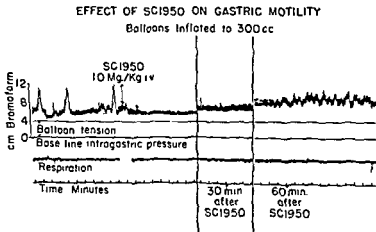


FIG 2—Gastrometric study demonstrating effect of SC 1950 on gastric tonus and contractile activity.

Intravenous administration of neostigmine 0.5 mg caused a return of gastric peristalsis in each of two patients tested following SC 1950, and intramuscular administration of 0.5 mg caused return of contractions of the stomach or reversal of the gastric effects of SC 1950 in one of two patients. I necholine 25 to 50 mg administered intramuscularly to four patients also reversed the action of SC 1950 and caused an increase of gastric tonus and return of contractions.

As a control for radio-graphic studies of action of SC 1950 in patients fluoroscopic and roentgenologic studies were performed after ingestion of barium on six patients with apparently normal gastrointestinal tracts. Gastric emptying was at least 50 per cent complete in one hour, averaging 70 per cent and was 98 to 100 per cent complete in two hours in these patients. Gastric peristalsis and emptying were normal to fluoroscopic examination.

On another day these same studies were repeated but SC 1950, 20 mg per kilogram, was administered intramuscularly 30 minutes prior to barium. Immediately after ingestion of barium, fluoroscopic study showed no peristaltic activity or gastric emptying and average gastric emptying was 25 per cent at 1 hour, 40 per cent at 2 hours and at 4 hours only two of the six had 100 per cent gastric emptying. In the control studies barium reached the cecum by 4 hours in all patients, but after SC 1950 it reached the cecum at 4 hours in only one of the six.

Four patients had continuous gastric aspiration through a Levine tube obtaining samples every 15 minutes over a 2 to 3 hour period. Intravenous administration of 10 to 15 mg per kilogram of SC 1950 caused marked decrease in volume of gastric content aspirated and decrease in values for free and total acid in the specimens with corresponding change in pH. Free acid was present in all specimens prior to SC 1950 but was absent in two or more specimens in three of the four patients after SC 1950 and markedly reduced in the fourth patient.

C 7337—The effect of C 7337 on the stomach was tested using 300 cc intragastric balloons in eight patients. C 7337, 10 to 15 mg per kilogram, was administered intravenously. No consistent effect was seen. There was no appreciable change of gastric tone or of resting intragastric pressure. In five of the eight there seemed to be slight or insignificant decrease of activity for eight to twelve minutes following injection. Contraction waves following C 7337 in four patients were of greater amplitude than those before drug but were less frequent in occurrence.

Roentgenographic and fluoroscopic studies of the gastrointestinal tract following ingestion of barium were performed in five patients who had no gastrointestinal complaints. Two received 75 mg (12 mg per kilogram) C 7337 orally 30 minutes before barium and three received 10 mg per kilogram C 7337 intravenously 15 minutes before barium. Gastric peristaltic activity and emptying were normal as observed fluoroscopically. Roentgenograms at intervals following fluoroscopy revealed a slight delay of initial gastric emptying in two, there being only 10 and 25 per cent emptying in 1 hour but complete emptying by 3 hours. Emptying rates of the others were within normal limits. Transit time through the small intestine was within normal limits in all five.

Continuous gastric aspiration with collection of samples at 15 minute intervals was performed in six patients. C 7337 10 to 15 mg per kilogram was administered intravenously after basal secretion had been measured for 1 hour or more. Following the drug five of the six had no significant change in milliequivalents of acid secreted during the 15 minute periods. The sixth had an

TABLE II SC 1950 AND C 7337 IN MAN

	SC 1950	C 7337
Administration	IV, IM (not oral)	IV, IM (oral)
Blood pressure	Reduced	Reduced
Cardiac rate	Slightly increased	Increased
Vascular reflexes	Blocked	Blocked
cold breath holding		
Temp gradients extrem	Blocked	Blocked
Gastrointestinal tone,		
peristaltic activity		
Balloon studies	Reduced	Little change
X-ray studies	Reduced	No change
Ca. line activity	Reduced	No change
Side effects	Flushing ptosis of lids dryness of mucous mem brane loss of accommoda tion	Flushing ptosis of lids nasal congestion

* A comparison of route of administration and effects. Each drug was administered parenterally in comparative studies

secretion of acid from an average of 0.47 meq per 15 minute period over a 11½ hour period before C 7337 to 0.71 meq per 15 minute period for a 11½ hour period after 10 mg per kilogram. The pH of the specimens changed from an average of 2.2 before the drug to 1.8 afterward. The average secretion of acid during the 15 minute periods decreased from 1.21 meq before C 7337 to 1.02 meq in the five consecutive 15 minute periods immediately following drug in all six patients.

For convenience mode of administration and effects of SC 1950 and of C 7337 have been summarized and compared in Table II.

C 7337 has been administered orally at intervals of 2 to 4 hours to thirty patients who have continued the drug for periods of from 24 hours to 4 months. These have included nine patients with Raynaud's disease, three probably with Buerger's disease, one with arteriosclerotic occlusive disease, thirteen with hypertension and three patients with atypical or cruralgia like pains in the extremities. Dose has varied from 25 mg every 4 hours to 100 mg every 2 hours. Since follow up has not been carried out on most of these patients long enough for complete evaluation, statement of effect of treatment will not be given. Results indicate however that the drug is usually well tolerated producing few side effects, and not producing abnormalities evidenced by blood counts or urine analysis.

DISCUSSION

Results of the studies described here and summarized in Tables I and II indicate that two new drugs, one 2,6 dimethyl diethyl piperidinium bromide (SC 1950), a ganglionic blocking agent and the other 2-(N-propyl-N-methyl-4-hydroxyphenyl)imidazoline hydrochloride (C 7337), an adrenergic or sympatholytic agent may be safely given to patients to produce effects which might be valuable in the treatment of certain diseases related to dysfunction of organs supplied by the autonomic nervous system. The first of these drugs SC 1950 resembles in most of its actions the tetraethylammonium ion or Flaxman blocking both sympathetic and parasympathetic divisions of the autonomic nervous system. The second drug C 7337 resembles in its actions

Priscol and Dibenzamine, blocking adrenergic pathways peripherally or at the end organ and therefore preventing the vasoconstricting or blood pressure elevating action of adrenalin and interrupting sympathetic nerve conduction without significant interference with the parasympathetic nerves. This drug is effective by oral administration.

CONCLUSION

Each of the two drugs described is apparently effective and well tolerated in patients.

REFERENCES

1. Grimson K. S., Reardon M. J., Marzoni F. A. and Hendrix J. P. The Effects of Priscol (2-Benzyl-4,5-Imidazoline HCl) on Peripheral Vascular Diseases, Hyper-
the
2. Searle Inc.
3. Longino, F. H., Chittum J. R. and Grimson K. S. The Effects of a Quaternary Amine on Functions of the Autonomic Nervous System. *Proc Soc Exper Biol & Med* 70: 46, 47, 1949.
4. Meier, R., Yonkman F. F., Craver B. N. and Gro F. A New Imidazoline Derivative With Marked Adrenolytic Properties. *Proc Soc Exper Biol & Med* 71: 70-72, 1949.
5. Chapman W. P., Stanbury J. B. and Jones C. M. The Effect of Tetraethylammonium on the Small Bowel of Man. *J Clin Investigation* 27: 34, 1948.

VENOUS PRESSURES IN THE SAPHENOUS SYSTEM IN NORMAL, VARICOSE, AND POSTPHLEBITIC EXTREMITIES

ALTERATIONS FOLLOWING FEMORAL VEIN LIGATION

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ALTHOUGH in recent years much progress has been made in improving the operative attack on conditions resulting from venous stasis in the lower extremities search is still being made for an operation which will insure normal venous return from the leg after this mechanism has been damaged by disease. Most procedures have consisted of the interruption, removal, or obliteration of incompetent or varicose veins in which the flow of blood is presumably reversed. Formerly these efforts were directed entirely at the saphenous system.^{8, 13, 16, 17, 20, 22} Such an approach was found to be adequate only in patients whose saphenous veins alone were incompetent. In patients whose deep or communicating veins had been damaged by phlebitis⁶ it was logical that attention was next directed to ligation of these veins in order to protect the skin and subcutaneous tissues against the noxious effects of increased pressures which were not normally relieved through the deep system.¹¹ More recently in such 'postphlebitic' extremities direct attacks on the deep system itself have been made.^{6, 10} Long term clinical results in patients so treated are not yet available.

The proposal to ligate the deep veins of any given lower extremity in which venous stasis exists inevitably raises certain questions. Are all deep veins which have been damaged by a past phlebitis and which have become recanalized not only totally incompetent in returning blood from the limb but also harmful and best interrupted? Are all superficial veins which are dilated under such circumstances *ipso facto* likewise incompetent and in need of removal or obliteration or are they compensatory in nature and accordingly useful? If we accept that femoral vein ligation is indicated in postphlebitic legs are the clinical tests of Trendelenburg and Perthes which are designed to demonstrate incompetency of the deep system so reliable that we can be sure of avoiding ligation of a normal femoral vein?

Answers to these questions and the evaluation of the various operative procedures have been difficult because available tests of venous function have depended upon visual or palpable estimates of venous distention which have been so rough as to have defied accurate numerical expression. The rate at which the veins of the leg fill below a tourniquet when the patient changes

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from a lying to a standing position (Trendelenburg) has been arbitrarily set at more than thirty seconds in order to indicate failure of reflux from the deep to the superficial system in the lower leg. Whether the limit of thirty seconds is proper or not, the estimation of the end point with fingers or eyes is approximate at best. The readiness with which the skin veins empty below a tourniquet when the patient is walking (Perthes), although in principle a better functional test, is also subject to similar criticism with regard to exactitude. In both these tests obesity or lack of prominence of veins may render impressions unreliable. A search for a more reliable test seems indicated.

Perthes¹⁸ in 1895 first observed that the pressure in the veins of the leg decreased on ambulation and that this did not occur in extremities with incompetent veins unless these veins were occluded above the area observed. He made his observations by using a rubber band around the calf which he could watch contract as the pressure fell. Ochsner and Mahorner¹⁷ stated that the pressure in varicose veins is greater than in normals. Rutledge¹⁹ found this to be true of "secondary" varicose veins and Mayerson, Long and Giles¹⁴ observed it only in the reclining position. Other authors, however, found little difference in resting venous pressures between varicose and normal extremities regardless of the position assumed (Adams,¹ Beecher,² and Seiro¹). Mayerson also found no difference in the standing position when the patient was at ease.

Those observers who have studied venous pressures in the lower extremity under conditions of exercise and straining on the other hand have found marked differences between normal and varicose extremities. Beecher using an indirect method of determining venous pressures by means of a celloidin capsule sealed to the skin⁴ found the pressures in normals to fall to between 28 cm and 75 cm during ambulation and was able to describe the alterations at various stages during each step. In varicose extremities the pressure during walking persisted at 96 cm, this reading being the same as before walking. Seiro²¹ using the direct method of Moritz and von Tabora¹⁵ observed that the standing venous pressures varied with respiration decreasing with inspiration and increasing with expiration. He also discovered that the pressure fell during walking in direct proportion to the competency of the saphenous valves and that if the valves were incompetent occlusion of the saphenous vein above the needle caused as great a fall of venous pressure on ambulation as if the valves were competent. Veil and Hussey³ performed similar tests on the popliteal vein and found marked rises in pressure during walking when there was obstruction of the deep system above due to thrombosis or pregnancy.

Delbet⁷ found a great increase in pressure on straining when the pressure in the saphenous vein in the thigh was measured directly by means of a mercury manometer. Adams¹ using the direct method found that straining in patients with varicose veins caused venous pressures as high as 224 mm of mercury and that that produced by straining after vein ligation in such a patient was 114 mm of mercury which was nearer the magnitude of pressure obtainable by straining in the normal.

These contributions suggest that the major circulatory defect in an extremity in which there exist incompetent veins is not a venous pressure which habitually reaches values higher than normal but a venous pressure which, like the normal is during resting, equal to the height of the column of blood between the heart and the area tested, but which, unlike the normal, fails to fall on muscular exercise. It also appears that the magnitude of pressures obtained on straining in patients with varicose veins is greater than in the normal.

The present study was made to discover whether determinations of venous pressure in the saphenous vein in the erect position both resting and walking as performed by Beecher and Sairo might serve as a more accurate Perthes test for venous function in the lower extremity. It was stimulated by the hope that the answers to some of the questions posed might be made clear.

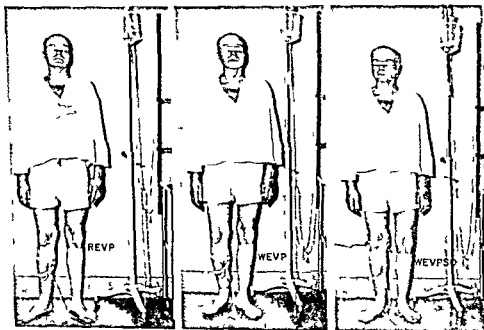


Fig 1—The venous pressure apparatus is shown in use with the patient standing still (REVP) with him walking (WEVP) and with him walking in the presence of saphenous vein occlusion (WEVPSO).

METHODS USED

The method used was that of Moritz and von Tabora (Fig 1). A venepuncture is performed in one of the saphenous veins of the calf or one of their tributaries with a No 20 gauge needle. This is connected by a rubber tube six feet in length to an elevated reservoir of physiologic salt solution which is allowed to drip continually into the vein except during the time that the pressure readings are being made. A side arm in the middle of this tube leads to a manometer which consists of a glass tube 60 cm in length with a bore of 3 mm fastened to a vertical centimeter rule. The manometer is filled with solution

from a lying to a standing position (Trendelenburg) has been arbitrarily set at more than thirty seconds in order to indicate failure of reflux from the deep to the superficial system in the lower leg. Whether the limit of thirty seconds is proper or not, the estimation of the end point with fingers or eyes is approximate at best. The readiness with which the skin veins empty below a tourniquet when the patient is walking (Perthes), although in principle a better functional test, is also subject to similar criticism with regard to exactitude. In both these tests obesity or lack of prominence of veins may render impressions unreliable. A search for a more reliable test seems indicated.

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femoral condyle, the external saphenous vein below the popliteal space, other points where communicating veins may seem clinically to be incompetent.*

The apparent difficulty of making comparisons between individuals of different heights, who normally would have different degrees of pressure fall during ambulation were found after numerous calculations to be insignificant with respect to the purpose of the test. Fig. 3 is a graph in which the fall of pressure in centimeters was plotted against the fall expressed in the percentage of the distance from the base line (the heart) and the floor. It is apparent that the factor of height in comparing two individuals of different heights would never lead to an error of greater than 10 cm. and then only when the fall was maximal. It was therefore, considered wise to persist in the more convenient method of expressing pressures namely centimeters of fall as read on the manometer.

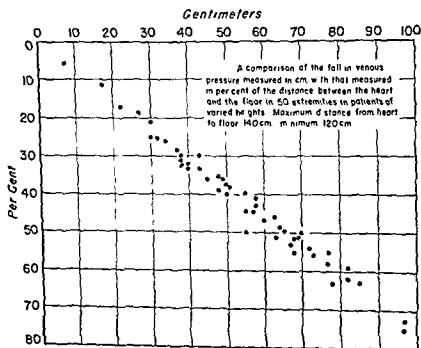


Fig. 3

The extremities tested fell in three clinical groups: normals, those having uncomplicated varicose veins, and those which showed postphlebotic stasis. The normal extremities were those causing no symptoms and possessing no prominent varicosities, although prominent straight veins did not exclude an asymptomatic extremity from the normal group. The varicose extremities were those which were symptomatic with large or small varices plus those with small varices which were asymptomatic. Often the dividing line between a normal and a varicose extremity was hard to draw. The postphlebotic extremities

Dr. F. J. Barrett and Dr. J. M. Carey, of the resident staff of the West Roxbury Veterans Hospital and Dr. J. L. Thompson, Dr. T. Brooks, and Dr. A. Rodkey, of the resident staff of the Massachusetts General Hospital gave valuable additional help in performing the tests.

from the reservoir, and the venous pressure reading is made by eliminating the reservoir from the system and allowing the fluid in the manometer to seek a level.

All readings were made in the erect position. The resting erect venous pressure was considered to be normal if the manometer level fell between the projection of the right auricle arbitrarily set at the space between the fourth and fifth costal cartilages, and 15 cm above it. In testing any individual extremity this point was then taken as 0, and all changes from it were expressed in centimeters of water as fall or rise.

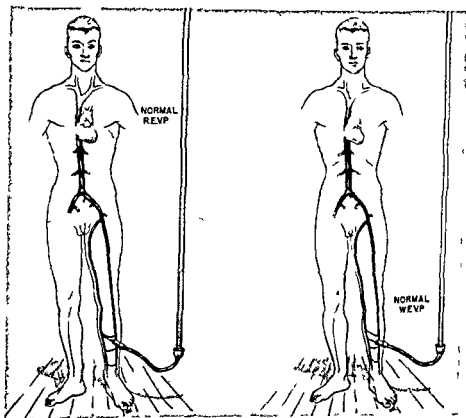


Fig 2—A diagrammatic illustration of the differences in venous pressure in the saphenous system of the normal lower extremity between the resting and ambulatory states.

Three pressures were ordinarily determined: the resting erect venous pressure (REVP), the walking erect venous pressure (WEVP), in which the patient walked in place at 120 steps a minute and the walking erect venous pressure during saphenous vein occlusion (WEVPSO) (Fig 2). Occlusion of the saphenous vein was always performed with the palpating finger. The value given is the greatest fall obtained as determined by testing occlusion at various points usually in the following order: the internal saphenous vein at the

the extremes. The standard deviation was 85 cm and the standard error of the average ± 4 cm.

Walking Erect Venous Pressure During Saphenous Occlusion (WEVPSO)
—The WEVPSO test was performed in 10 normal, 74 varicose and 12 post phlebitic extremities.

Normal extremities. The average change of pressure during the test in normal extremities was -45.2 cm with a maximum of -72 cm and a minimum of -25 cm. The standard deviation was 12.7 cm and the standard error of the average ± 4.0 cm. In 6 extremities the occlusion of the saphenous vein caused no change in pressure from the WVP without occlusion. In 2 there was a further fall on occlusion. In 2 there was a rise above the WVP level.

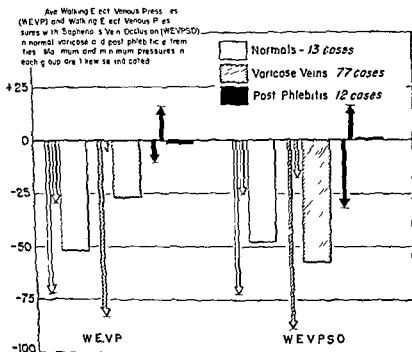


Fig. 4

Varicose extremities. An average fall of -57.2 cm took place in the varicose extremities with extremes of -18 cm and -85 cm. The standard deviation was 14.3 cm and the standard error of the average ± 1.7 cm. In each patient this reading was lower than in the same test in that patient taken during walking without saphenous occlusion.

Postphlebitic extremities. During the test in postphlebitic extremities the average change in pressure was a rise of $+0.66$ cm. The standard deviation was 17.5 cm and the standard error of the average was ± 3.8 cm. In only 1 patient of this group did this test show a lower fall than in the same test without saphenous occlusion. This occurred in a patient whose WVP was -2 cm but whose WEVPSO was -20 cm. In spite of a definite history of milk leg how

ties were those with a past history of phlebitis and current venous stasis. In these the Trendelenburg test and the Perthes test tended to indicate poor function of the deep system. In many, phlebograms were done which showed failure of filling or lack of valves in the system, and in most the femoral vein was biopsied at operation and shown to have been damaged by past inflammation.

In order to determine whether it is always important to use the same vein on repeat tests in the same extremity, a group of observations were made with two simultaneous recordings in different veins in the same extremity. Observations were made in 3 normal extremities. If D equals the vertical distance between the two needles and F is the difference in WVP in the two manometers, the ratio D/F should be a constant one in different subjects in order to enable us to make a calculation to correct for a different level of the needle on repeat tests in any case. In our 3 patients the ratio D/F was $34/14$, $32/32$ and $45/15$. In other words although the fluid level in the manometer attached to the lower needle fell to a point which was nearer the floor than that in the higher needle it did not always do so in predictable amounts. Simultaneous tests were also made at two different points in 14 varicose or postphlebotic extremities. Here also the additional fall in pressure found in the lower vein was noted but was unpredictable in amount. Therefore we have concluded that the same vein must be used on all repeat tests in the same patient.

RESULTS

Resting Erect Venous Pressure (RFVP)—The RFVP was determined in 102 extremities. In 13 of these the veins were normal, in 77 varicose and in 12 postphlebotic. In all but 2 of these extremities the fluid level came to rest between 1 cm. and 15 cm. above the fourth and fifth right costal cartilage. In 1 of these patients a stable level of pressure could not be found while testing the normal leg because the patient was nervous, could not stand still and had a marked postural sway. In the other of the 2 exceptions we were concerned with a patient with varicose veins who had asthma and whose recumbent venous pressure was 25 cm. above the level of the right auricle. The RFVP in his case was 20 cm. above the fourth right costal cartilage.

Walling Erect Venous Pressure (WVP)—The WVP was determined in 13 normal, 77 varicose and 12 postphlebotic extremities. Fig. 4 demonstrates a comparison between the results in these three groups in terms of maximum, minimum and average change.

Normal extremities—There was an average change in normal extremities of -51.7 cm. with extremes of -28 cm. and -72 cm. The standard deviation was 13.5 cm. and the standard error of the average ± 3.8 cm.

Varicose extremities—The average change of pressure in the varicose extremities was -26.6 cm. with extremes of -3 cm. and -82 cm. The standard deviation was 16.9 cm. and the standard error of the average ± 2.4 cm.

Postphlebotic extremities—The average change in pressure in postphlebotic extremities was -1.8 cm. A maximum fall of -10 cm. and a rise of $+16$ cm. were

the extremes. The standard deviation was 8.5 cm and the standard error of the average ± 2.4 cm.

Walking Erect Venous Pressure During Saphenous Occlusion (WEVPSO)
—The WEVPSO test was performed in 10 normal, 74 varicose and 12 post-phlebitic extremities.

Normal extremities The average change of pressure during the test in normal extremities was -45.2 cm with a maximum of -72 cm and a minimum of -25 cm. The standard deviation was 12.7 cm and the standard error of the average ± 4.0 cm. In 6 extremities the occlusion of the saphenous vein caused no change in pressure from the WFVP without occlusion. In 2 there was a further fall on occlusion. In 2 there was a rise above the WFVP level.

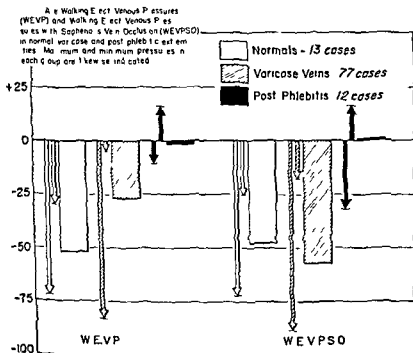


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over, the superficial femoral vein showed at operation only minimal evidence of past inflammation and may have been normal. In 1 of the other 11 extremities there was no further change in pressure when the saphenous vein was occluded. In the remaining 10 extremities saphenous occlusion resulted in a venous pressure in the saphenous vein which was 1 cm. to 10 cm. higher than that without occlusion.

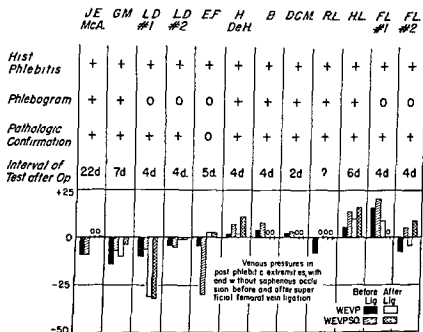


Fig 5

Influence of Femoral Vein Ligation on Postphlebotic Stasis.—In 12 post phlebotic extremities pressure determinations were made after superficial femoral vein ligations. These were compared with those made before ligation in the same patients. They were all done within one month after the procedure, most of them within the first week postoperatively. Fig 5 shows the variations in the WEVP with and without saphenous occlusion between the pre and post operative states. In 5 of the extremities the WEVP was higher in the post operative state than in the preoperative. This increase in pressure on walking was not great, the maximum being 7 cm. In 3 extremities there was no change in WEVP after ligation and in 4 there was a fall. In all but 1 of the instances in which a fall occurred it was insignificant in degree (20 cm. more than before operation). If the saphenous vein was occluded during walking in the post ligation extremity there was no pressure recorded which was lower than the pressure prior to occlusion in any case. In 7 extremities there was no change in pressure and in 5 there was a further rise.

Comment.—A quantitative expression of the differences in the function of the venous systems in the lower extremities of patients with normal, varicose

or postphlebotic venous circulations, is shown in terms of average figures in Fig. 4, reveals that the patient with a normal extremity can, on the average, lower the pressure in the saphenous vein by walking by the vertical distance between the heart level and the level of the upper thigh. The extremity with uncomplicated varicose veins can, on the average, do only about half this well, whereas the postphlebotic extremity can lower it essentially not at all. Occlusion of the saphenous vein does not greatly alter the pressures in the normal or the postphlebotic leg but will drop the pressure in uncomplicated saphenous varices to a level which in our group was even lower than the normal.

The tests have revealed that clinical judgment in pricing the extremities in the 3 groups was occasionally faulty since as is shown in Fig. 4 each group has some extremities in it which according to venous pressure reactions, do not belong there. The extremes of fall on WEVP in normal extremities were 25 cm and 72 cm. In varicose extremities they were 3 cm and 82 cm respectively. It seems obvious from these tests that the patient in whom the pressure fell 82 cm on walking, without occlusion had good venous function even though the veins were prominent and showed a few small varices. On the other hand in the patient with the normal extremity whose WLVP was only -28 cm and showed a WLPSO of -45 cm one could postulate that although no varices were seen, the saphenous vein is already incompetent and frank varices may develop in the future.

The same difficulty may be encountered in making the diagnosis clinically between a varicose extremity and one which has had phlebitis. On this point the chief value of the test lies in the fact that the average WEVPSO in the varicose extremity was -57.2 cm whereas there was no fall in the postphlebotic group.

With regard to the early postoperative results following femoral vein ligation for postphlebotic stasis these tests have in most cases, shown little improvement in venous function. It is to be emphasized however that these observations were made in the early postoperative period and that any beneficial effect which femoral vein ligation may have could conceivably not be manifest for several months or until the collateral circulation through subcutaneous and muscular veins has had time to develop. Studies of this are being made at present.

Only partial and preliminary answers can be given to the questions posed earlier in the paper. The studies on postphlebotic extremities before and after operation suggest that deep veins which have previously been damaged by disease are incompetent but that ligation of them does not give dramatic improvement in venous function. They also suggest that in many postphlebotic extremities the saphenous veins although prominent and slightly varicose may perform a useful though incomplete, function. The answer to the third question as to whether this test can give better information with regard to the function of the deep system than tests dependent on visual or tactile estimations of venous filling has in our opinion been given in the affirmative. All extremities operated upon which have shown faulty function in the deep veins according to these tests have demonstrated abnormal femoral veins at operation.

ever, the superficial femoral vein showed at operation only minimal evidence of past inflammation and may have been normal. In 1 of the other 11 extremities there was no further change in pressure when the saphenous vein was occluded. In the remaining 10 extremities saphenous occlusion resulted in a venous pressure in the saphenous vein which was 1 cm. to 10 cm. higher than that without occlusion.

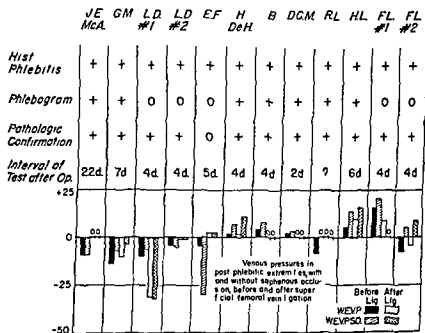


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The tests have revealed that clinical judgment in placing the extremities in the 3 groups was occasionally faulty since as is shown in Fig 4, each group has some extremities in it which, according to venous pressure reactions, do not belong there. The extremes of fall on WVP in normal extremities were 28 cm and 72 cm. In varicose extremities they were 3 cm and 82 cm respectively. It seems obvious from these tests that the patient in whom the pressure fell 82 cm on walking without occlusion had good venous function even though the veins were prominent and showed a few small varices. On the other hand in the patient with the normal extremity whose WVP was only -28 cm and showed a WVP SO of -45 cm one could postulate that although no varices were seen the saphenous vein is already incompetent and frank varices may develop in the future.

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There are two points with regard to the technique of the test which, although not apparent in the figures, seemed significant while the tests were being made. First, the *rapidity of pressure changes* which took place during ambulation varied widely in different extremities. The responses in the postphlebotic extremities were notoriously slow and sluggish; those in normal and in varicose extremities after saphenous occlusion were rapid and definite. Responses also tended to vary in speed in the same extremity in inverse proportion to the length of time the patient had been in the erect position prior to the test. Second a difference between two readings of a few centimeters must be considered without great significance unless it is repeatable. Factors introduced by involuntary straining and by failure to stand erect combined to make us feel that it is better to interpret changes as significant in terms of five or tens of centimeters rather than of single centimeters. The standard deviations of between 8.5 and 16.9 cm. in the data which make up Fig. 4 are expressions of this.

It must also be remembered that the direct method of determining pressures does not detect the rapid changes which have been shown by Lecher to take place during a single step. The levels here observed must be considered to represent averages maintained for several steps. This may, however, be advantageous in estimating the over all effect of the venous return.

The measurement of venous pressure in the saphenous system of veins of the lower extremity during walking does not introduce a new concept into the understanding of venous stasis in the leg. It does, however, re-emphasize the importance of the circulatory defect in this condition as has been previously done by Perthes, by Beecher, by Seiro and by Adams. We have attempted to adapt their work to problems as we see them in the clinic. The method which is simple in conception but occasionally cumbersome in execution due to difficulty in keeping the recording needle securely in a vein is not to be recommended for the routine testing of all clinical cases of varicose veins. It is more adapted to the study of limbs in which the presence or absence of incompetency of the deep system is in doubt. In these patients a more accurate Perthes test can thus be done and by it the results of therapy can be checked.

SUMMARY

1. A method originally described by Beecher and by Seiro for the evaluation of venous stasis in the lower extremity was used to test 102 extremities. It consists of measuring the venous pressure in the saphenous system while the patient is in the erect position and comparing the values found on standing still with those on walking with and without digital occlusion of the saphenous veins.

2. The average fall of pressure on walking without saphenous occlusion was 52 cm. in normal extremities, 27 cm. in varicose extremities and 2 cm. in postphlebotic extremities. In varicose extremities occlusion of the saphenous vein during walking increased the fall in pressure to normal values (-57 cm.) whereas in normal and postphlebotic extremities the pressure fell slightly less well on walking with occlusion of the saphenous vein than without it.

AN IMPEDANCE GAUGING SYSTEM FOR MEASUREMENT OF BIOLOGIC PRESSURE VARIABLES

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PROJECTED cardiovascular and cardiopulmonary studies at the University of Kansas Medical Center made necessary the development of a new gauging system for the measurement of biologic pressure variables. This work is to be carried out on laboratory animals as well as on patients in different geographic areas of the Center. The problem was further complicated by our desire to study animals and patients during operations within the major body cavities. A fixed optical system thus seemed impractical. Piezometers are generally used in industry, however, until recently only a few have been employed in biologic studies. Best known of these devices is the unbonded resistance wire strain gauge. Use of this type of instrument was abandoned because of technical difficulties in construction and questionably adequate frequency response. Capacitance gauges have the advantage of high frequency response and simplicity in construction, however, they are unstable due to lead motion causing varying shunt capacity. Piezo electric crystals are unsatisfactory for this application since they fail to indicate static pressure. Because of high output and high frequency response, the displacement sensitive vacuum tube is well suited for biologic pressure measurements. We have not had an opportunity to evaluate this method. An impedance gauging system has these advantages: desirable physical characteristics, relative simplicity in construction and operation and adequate sensitivity and frequency response. The system which is to be described is the result of a cooperative venture by our electronics laboratory and an instrument company* and the gauge is now being manufactured by the latter organization.

The gauge consists of two coils surrounding an axially placed iron slug (Fig. 1). These two coils make up adjacent arms of an impedance bridge. The other two arms of the bridge are represented by a center tapped adjustable resistor. A third coil excited by a 5,000 cycle carrier is situated between the pickup coils. The iron armature is fastened to the center of the gauge diaphragm. At zero pressure the bridge is balanced for zero signal output. The output is then taken from the outer terminals of the paired pickup coils and is fed through a transformer to the first grid of the channel amplifier (Fig. 2). As pressure is applied to the diaphragm the armature moves in relation to the coils unbalancing the bridge and causing a signal to appear at the amplifier input. The magnitude of the signal is directly proportional to the applied pressure. This signal appears as an increasing or decreasing level of the 5,000 cycle carrier. After suitable amplification the carrier is demodulated leaving only the pressure wave envelope. This voltage is then applied to a galvanometer in the recording oscillograph. A cathode ray tube with long persistence screen

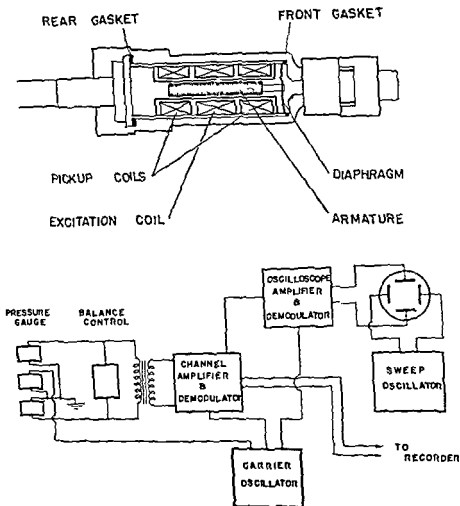
*Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 4 & 5, 1949.

This work was made possible by a grant from the Emergency Commission of the State of Kansas.

The Hathaway Instrument Company of Denver, Colo.

is used for monitoring this pressure wave. To obtain the relatively high voltage required to excite this tube, an additional amplifier and demodulator are employed. For adequate comparison of several successive pulse waves a low frequency sweep oscillator is used. It may be adjusted to sweep as slow as 2 cycle

Fig 1



Fig

Fig 1—Schematic drawing of the pressure gauging element
Fig 2—Block diagram of the gauging system.

per second thus permitting visualization of pulse waves during any five second period. Our present instrument is capable of synchronously recording five pressure variables. The gauge may be calibrated against a mercury manometer for a standard deflection on the record and on the cathode ray tube. After this adjustment has been made a switch permits attenuation of the deflection sensitivity in the following proportions: 0-100, 0-200, 0-100, 0-50, and 0-25. To attain perfect balance a variable resistor and capacitor are regulated from the

instrument panel. Inductive balance is obtained in the gauge itself. An output balancing control is also available on the instrument panel, this allowing precise composition of the oscillograph record.

The pressure sensing element is housed in a steel cylinder to the front of which the gauge diaphragm is sealed (Fig. 3). Leads emerge from the opposite

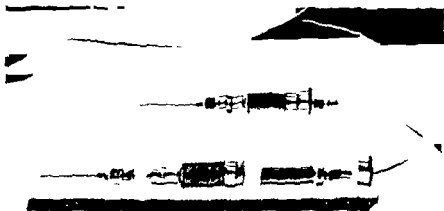


FIG. 3.—ICSA impedance gauge shown assembled above and below from left to right a standard needle, the glass shield with adapter, the steel cylinder containing the pressure-sensing element and the lead connector together with its threaded collar.



FIG. 4.—Three assembled gauges shown plugged into the junction box at right which is in turn connected to the control unit in the lower part of which three channel amplifiers are seen.

Fig 5

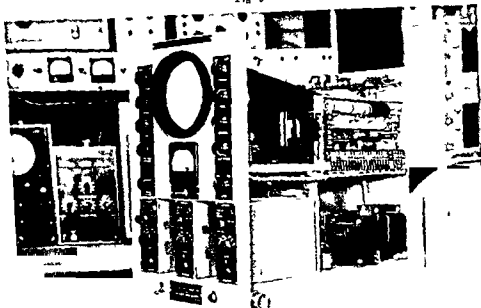
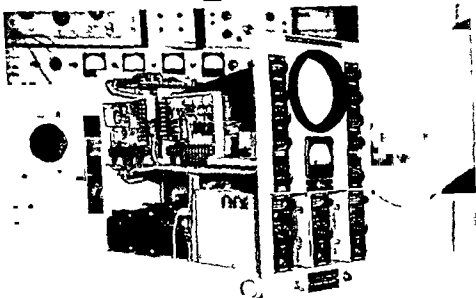


Fig 6



swing the common carrier oscillator
ray tube and its controls. Three
the amplifier and sweep oscillator

end of the cylinder, which is also sealed. The cylinder snugly fits a shortened 2 cc glass Luer syringe, the residual chamber being isolated to the diaphragm face by means of a front and rear gasket. The cylinder is held firmly against these gaskets by means of a threaded collar. The light flexible gauge lead is fifteen feet long and is fitted with a four terminal plug. This entire unit has been designed to withstand either hot or cold sterilization routines.

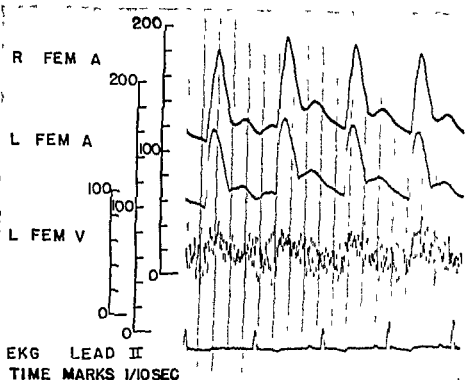


Fig. 1—Oscillograph record of blood pressure in a dog with an experimental fistula. The high amplitude is proximal to the fistula and the low amplitude is distal. The EKG is normal. Both sides of the fistula show a normal pressure.

All five gauges may be plugged into a junction box, which in turn is connected to the control unit containing the five channel amplifiers, the common carrier oscillator and the cathode ray tube together with its controls, amplifier and sweep oscillator (Figs 4, 5 and 6). Each amplifier may simply be pulled out of the controller to be replaced by one with similar characteristics or one of different design such as might be employed in electrocardiography. A multi-channel controller to the recording oscillograph are various work areas in the hospital are connected to a multi-channel coaxial cable of 600 feet maximum length.

Static response of this system has been found linear over the range of 0-400 mm of mercury (Fig 8). The natural frequency of the fluid filled gauge is in excess of 600 cycles per second. When fitted with a 20 gauge needle one and one-quarter inches long the frequency response is flat to 100 cycles per second

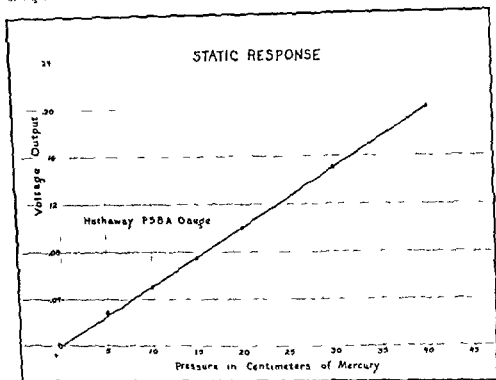


Fig 8—Static response of the P58A impedance gauge

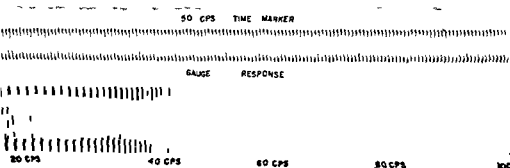


Fig 9—Frequency response of the P58A impedance gauge

(Fig. 9) A phase lag of about 30 degrees appears at 100 cycles per second. This phase distortion will not be apparent on any records likely to be made in connection with biologic investigations.

The writers wish to express their appreciation for the interest and cooperation of Mr. C. M. Hathaway and Mr. Warren Thibon of the Hathaway Instrument Co., Prof. H. C. Roberts of the University of Illinois and Mr. Oliver Boutrous.

FACTORS AFFECTING THE DIAMETER OF LARGE ARTERIES WITH PARTICULAR REFERENCE TO TRAUMATIC SPASM

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SIGNIFICANCE OF THE PROBLEM

SPASM of large arteries has long been recognized as a clinical condition following trauma in the neighborhood of the vessels or directly to them and it has been called by many names such as traumatic arterial spasm, myogenic spasm, or "arterial stupor"

Traumatic spasm is a well known complication of fractures particularly at the elbow joint, where Volkmann's ischemic contracture may be an end result. Dissection of a large artery such as the femoral during the operation of femoral vein ligation or for purposes of arteriography, may produce spasm as may the injudicious application of a tourniquet or a near miss by a projectile such as a rifle bullet.^{1,2}

Opinion is divided as to the exact mechanism of production of the condition and particularly as to the role played by nervous components. No really efficacious form of treatment has been yet devised and this is not surprising when the scant knowledge of the physiology of large arteries is considered.

PREVIOUS WORK

The clinical side of the problem has been considered at length by many authors. Reports of large artery spasm following the near passage of fast projectiles were numerous during World War I when the condition was sometimes referred to as Kroh's arterial stupor. More recently other authors Cohen,³ DeBakey and Simeone,⁷ and Griffiths⁸ have been interested in the subject and good bibliographies have been compiled.

Fundamental experimental work on the physiology of large vessels has been more scant than clinical observations. Lister⁹ performed some experiments on the effect of changes in blood pressure on the diameter of large arteries, finding a direct relationship between the diameter of large arteries at systolic and diastolic pressure as they pulsated and therefore concluded that alterations in blood pressure did not affect the width of arteries. This is a conclusion with which our experimental findings are at variance.

MacWilliam¹⁰ of Aberdeen in 1902 published the results of experiments on large arteries excised from oxen. Mechanical trauma was found to produce spasm but electrical stimulation in various forms had no effect except

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for very strong galvanic currents which were found to cause contraction. Many of his investigations such as the effects of extreme heat and cold and the application of various chemicals, however, bore little resemblance to physiologic or therapeutic measures besides carrying the disadvantage of being *in vitro* experiments. Grant¹¹ recorded the effects of various stimuli upon the arteries of the rabbit's ear observed through a microscope and although these vessels are considerably smaller, they often behaved in a similar way to the larger arteries such as the femoral observed in this study.

More recently attention has been focused upon the question of nervous reflexes causing large artery spasm (Barnes, Trueta, and others^{12, 13}). These workers investigated the role of vascular factors in the crush syndrome by applying tourniquets to the limbs of rabbits and visualizing the arterial tree by means of radiopaque injections. They were able to demonstrate a shrinkage of the arterial tree in the leg contralateral to the tourniquet and concluded that this was due to a nervous reflex.

Both local and reflex spasm have been investigated in the experiments which will be described here.

METHODS

The techniques used in the present study will be outlined before the experimental results are recounted. Rabbits and cats were used. Endotracheal cannulation, bilateral vagotomy, and division of the cervical sympathetic were performed as a routine.

Measurement of the Arterial Diameter—Most observations were made upon the femoral artery of rabbits or cats just below the inguinal ligament. The artery was exposed by making a short transverse incision through the skin and deep fascia and by careful dissection with a sharp scalpel defining its borders for about one quarter inch in extent. A thin layer of voluntary muscle overlies the femoral artery in the rabbit and this had to be removed. Care was taken to leave as much connective tissue as possible around the artery in each case so that any possible periarterial nerve plexus in the adventitia was left intact.

In those cases in which the effect of mechanical trauma was being studied the dissection was carried beneath the artery as well so that a length of cotton thread could be passed under it and used to give the artery a sharp stretch.

In certain cases where it was desired to exclude nervous factors the adventitia was removed during the dissection which was carried up and down the artery for a somewhat greater length. This for example was the routine method of dissection in those cases where reflex spasm was being studied and for which sympathectomy had been performed to exclude nervous mechanisms.

In order to avoid drying of the arterial or surrounding tissues they were kept covered by a shallow pool of liquid paraffin. Visualization through this was good and the lateral edges of the artery were well defined.

When the effects of agents such as electrical stimulation or mechanical trauma applied directly to the arterial wall were being studied, the liquid

paraffin could not be used and instead the tissues were kept moistened from time to time with drops of physiologic saline solution.

In the preliminary exploratory experiments naked eye observation of the artery was used but in the majority of cases a Bausch and Lomb dissecting microscope with a Zeiss micrometer eyepiece was employed. Magnification in the region of 10 times was obtained and measurements could be made to two decimal places of a millimeter. No unduly bright or close source of light was necessary so that problems of heating by the light source did not arise.

Measurement of Paw Volume—In most animals information about the state of the peripheral circulation concomitant with large vessel changes was obtained from plethysmographs applied to the paws. These consisted of glass tubes connected to recording devices writing upon smoked paper on a kymograph. Water baths surrounded the glass tubes to nullify the effect of fluctuation in room temperature and it was endeavored to keep this as constant as possible. A record was kept of room temperature during the experiment so that effects due to any marked changes could be known and excluded. The volume of paw included in the plethysmograph was usually about 40 cc and an airtight seal was made between the plethysmograph and the closely clipped skin of the limb with a glue made of printer's compound. Leakage was carefully tested when the apparatus was first set up and corrected if present.

Tourniquets—Parts of the investigation of reflex spasm consisted of a series of tourniquet experiments on rabbits similar to those performed by Trueta and his co-workers^{12, 13} and an exactly similar method of application of a rubber covered wire tourniquet was used. After a number of experiments some disadvantages of this technique became evident: congestion of the veins of the leg always occurred as it is impossible to tighten the wire rapidly. Furthermore, the artery lying between the femur and tibia is hidden over which the wire passed is protected and arterial occlusion often did not occur at once but only after some swelling of the limb had taken place through venous obstruction. This made uncertain the exact duration of arterial occlusion allowed local swelling to take place before release of the tourniquet and caused the animal to get a small transfusion of stagnant blood when the wire was released.

It was thought that a simple rubber arterial tourniquet applied to the thigh just below the tuber ischi was more simple and desirable and this was adopted for the later tourniquet experiments. An Esmarch bandage was tightly applied to the limb before the rubber tourniquet in order to avoid venous congestion.

Blood Pressure Records—The carotid blood pressure was recorded during the experiments by means of a glass cannula (coated with "Dri-film" to help prevent clotting) tied into the right common carotid artery and connected by a system filled with 3 per cent sodium citrate to a mercury manometer writing upon a smoked drum.

Anesthesia—Intraperitoneal Nembutal supplemented by open ether when necessary, was used on the first animals in the tourniquet experiments in the same way as Trueta and his co-workers¹⁻³ had used it. Nembutal acts only for about seventy-five minutes and therefore requires repetition. Open ether causes fluctuations in blood pressure and secondary effects upon the vascular system. In the later tourniquet experiments, therefore, longer acting anesthetics which gave a steadier preparation with less rapid deterioration were used. Intravenous 25 per cent urethane 8 cc per kilogram body weight, was employed or in cases where no reflex activity was being investigated Dial urethane •07 cc per kilogram intraperitoneally, was used.

EXPLORATORY EXPERIMENTS

A variety of different maneuvers was carried out and the effects observed by the naked eye on the femoral artery of both sides (see Table I). Some of these procedures were then selected for study in greater detail.

Is Large Artery Spasm Always Accompanied by Spasm of Collaterals? In most of these experiments concomitant limb volume records were made with plethysmographs on the paws. Spasm of the femoral artery produced by mechanical trauma did not affect the volume of the paw on the same side or at least no more than simple ligation did. This finding is inconsistent with the view sometimes advanced that active spasm of the whole arterial tree follows segmental spasm of a large artery. On the other hand decrease in limb volume did occur if the spasm extended sufficiently far along the artery to include the openings of branches.

TABLE I RESULTS OF EXPLORATORY OBSERVATIONS

EVENT		EFFECT ON DIAMETER OF FEMORAL ARTERY (NAKED EYE OBSERVATIONS)	
		SAME SIDE	OPPOSITE SIDE
1	Mechanical trauma (longitudinal or transverse)	Decrease	Nil
2		Decrease	Decrease
3		Nil	Nil
4		Nil	Nil
5		Nil	Nil
6		Nil	Nil
7	Faradic stimulation to central end of femoral nerve	Nil	Nil
8	Faradic stimulation to femoral vein	Nil	Nil
9	Mechanically produced spasm of femoral vein	Nil	Nil
10	Ligation of femoral vein	Nil	Nil
11	Faradic stimulation directly on intact femoral artery	Nil	Nil
12		Nil	Nil
		Dilatation	Not observed

How Does the Behavior of Other Large Arteries Compare With the Femoral? The effects of some of the factors listed in Table I were also observed in large arteries other than the femoral. Repetitive electric stimuli of various

characteristics were applied to the upper and lower abdominal aorta the carotid, and the iliac arteries of rabbits and cats. In no case was significant narrowing observed.

Response to mechanical trauma such as that produced by a sharp jerk with a thread placed under the artery is recorded in Table II for different arteries. Sections of these arteries were removed from the animals and examined microscopically after staining with hematoxylin and eosin or Masson's stain. The amount of elastic and fibrous tissue present in proportion to muscle was much greater in the arteries in which spasm was difficult to produce. Complete occlusion by traumatic spasm could not be produced at all in the aorta which has a high proportion of fibrous tissue. It also has a high blood pressure, a factor which was studied more closely in the detailed experiments.

It is interesting to note that John Hunter¹⁴ observed that the larger arteries of the cow's placenta contracted less easily than the smaller ones.

DETAILED EXPERIMENTS

Factors affecting arterial diameter which were chosen for more detailed study fell under two headings: (1) those acting directly upon the vessel such as changes in blood pressure, mechanical trauma, or the possible effect of vasomotor nerves; (2) nervous factors acting reflexly from other parts of the body.

The first group was studied in both cats and rabbits using the techniques already described of direct observation of the diameter of the femoral artery with concomitant limb volume records by plethysmographic means.

Reflex arterial spasm was studied particularly in rabbits in a series of tourniquet experiments in each of which the behavior of the right femoral artery

TABLE II. PRODUCTION OF SPASM BY MECHANICAL MEANS IN VARIOUS ARTERIES OF THE RABBIT AND THE CAT

EASE OF ELICITING SPASM	ARTERY
1. Produced easily	Femoral, brachial
2. Produced with slight difficulty	External iliac, common iliac
3. Produced with great difficulty	Abdominal aorta, common carotid

and limb volume was studied in response to a tourniquet applied to the left thigh. This was done first on animals with an intact nervous system and later on animals in which parts of possible nervous reflex pathways had been excised.

Influence of the Blood Pressure on the Diameter of Large Arteries.—It was noticed quite early in these investigations that arteries became gradually smaller during the course of the experiment as the animal's condition deteriorated and that finally

very narrow indeed. This was especially true in those animals in which the lumbar sympathetic chain was removed. In those in which the nervous system was intact, these gradual changes in diameter were studied in greater detail in the tourniquet experiments which will be described later.

The effects of more rapid variation in blood pressure upon the artery produced by a variety of agents were studied. Intravenous injections of



Fig. 1—Cat anesthetized with intraperitoneal Nal (Clba 0.5 cc per kilogram) Injection of 1 cc of 1:50,000 adrenalin at third signal. Records from above down: diameter of right femoral artery; carotid blood pressure; volume of right hind paw; time signals at ten second intervals. All other signals refer to points at which arterial diameter was measured. Changes in the arterial diameter follow the blood pressure.

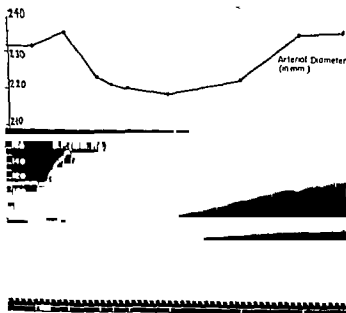
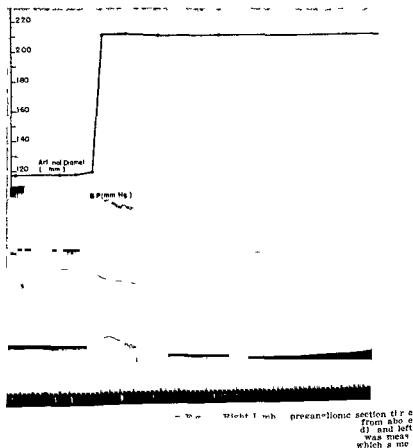


Fig. 2—Cat anesthetized with urethane (8 cc of 20 per cent solution intravenously). Right lumbar ganglionectomy one hour previously. Intravenous injection of 1 cc of 1:50,000 adrenalin at second signal. Records as in Fig. 1.

adrenalin producing a rise in blood pressure caused a parallel increase in diameter of the artery. This occurred in both the intact and sympathetomized limb (see Figs 1, 2, and 3). The limb volume shrinks in a sympathetomized limb but swells in the intact one following adrenalin injection. In the latter case the vessels are presumably constricted to start with and the increase in limb volume is purely passive. Faradic stimulation of the central part of the cut brachial plexus produced a reflex rise in blood pressure and the diameter of the artery was seen to enlarge simultaneously and shrink to its former size as the blood pressure fell once more (Fig 4).



Fluctuations in blood pressure due to the administration of open ether caused parallel changes in arterial diameter. Fig 5 shows how the diameter decreased when fall in blood pressure occurred after administration of open ether.

Intravenous injections of Nembutal produced a fall in blood pressure with parallel narrowing of the artery (see Fig 6). The pressure and diameter

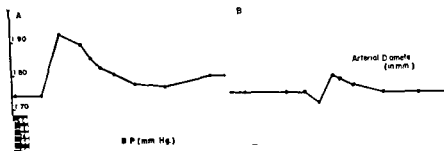


Fig 4—Rabbit anaesthetized with urethane (8 c.c. of 1 per cent solution intravenously) A 5 volts in primary B 3½ minutes after A 4 volts secondary coil (Harvard inductorium) at 5 cm. A trenzils intact. Order of records as in Fig 1. Faradic stimulation of brachial plexus center II causing reflex blood pressure changes. The diameter of femoral artery follows the change in blood pressure.

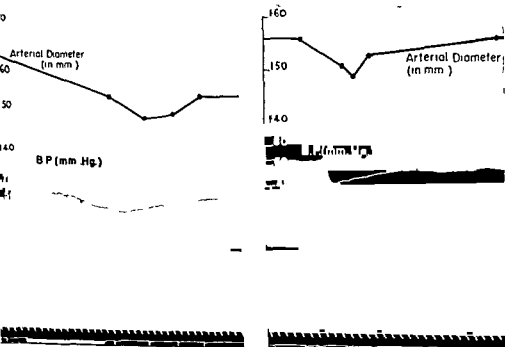


Fig 5

Fig 6

Fig 5—Rabbit anaesthetized with intraperitoneal ether vapour by inhalation at 1 mg signal diameter was measured. The blood pressure further injection of Nembutal intravenously Fig 1. Blood pressure and femoral artery

variations occurring with ether and Nembutal influenced our choice of anesthetic agents for the later tourniquet experiments

Other agents producing a fall in blood pressure such as Priscol or injections of adrenalin following Priscol,* produced the same fall in arterial diameter. The changes in arterial diameter with all the different drugs or mechanisms altering blood pressure indicated that the vessel behaved passively like an elastic tube. On some occasions, however, a somewhat different type

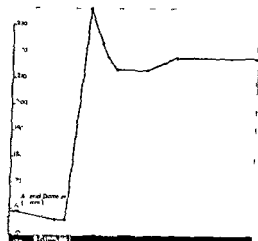


Fig. 7.—Rabbit anesthetized with Nembutal intraperitoneally (0.1 cc per kilogram) Adrenalin 0.1 cc intravenously at fourth signal. Order of records as in Fig. 1. This illustrates release of the ratchet mechanism of smooth muscle fibers which sometimes take up a new resting length with increase in blood pressure.

of change occurred in response to pronounced or prolonged rise in blood pressure produced by slow intravenous administration of adrenalin the artery rapidly dilated to almost twice its former diameter and remained at this size varying by the usual amounts from this new diameter with subsequent blood pressure variations (see Figs. 3 and 7). This suggested that the muscle fibers had taken up a new resting length and that some mechanism similar to the 'ratchet' mechanism of bivalves had been released.

Nervous Control of Large Artery Diameter—Electric stimulation of the lumbar sympathetic and of the artery itself was used to attempt to dem-

onstrate changes in diameter. The blood pressure was recorded in all these experiments in order to exclude diameter changes due to its variation. The lumbar sympathetic trunk was isolated and divided as high as possible where it first appeared in the abdomen from under cover of the diaphragmatic crus. Electrodes were placed under the chain just below this point of section; the abdomen closed and the blood pressure allowed to stabilize. This high position on the chain was chosen to ensure that stimulation occurred from the first and second lumbar ganglia which might supply fibers to the femoral artery downward. Repetitive electric stimulation with an electronic stimulator* was then applied in voltages varying from 2 to 20, usually using a biphasic current of 0.5 to 2.0 milliseconds duration at a frequency of 30 per second. Effective sympathetic stimulation was evident in the rabbit and cat by

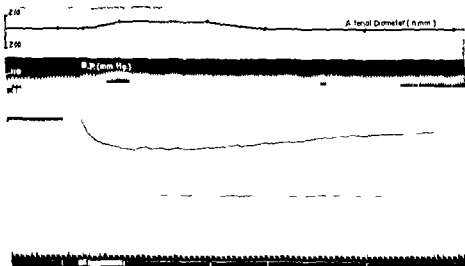


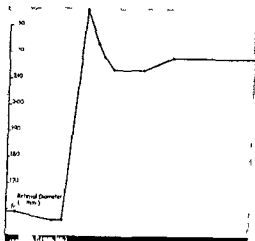
Fig. 8.—Cat anesthetized with urethane (4 cc. of 10 per cent solution intravenously). Long signal: electric stimulation of right sympathetic chain in region of first lumbar ganglion (10 volts biphasic duration 1 millisecond frequency 30 per second). The right femoral arterial diameter increases very slightly with the blood pressure. The right leg volume shrinks. Left leg volume (lower trace) unchanged.

shrinking of the volume of the limb in the plethysmograph and also in the cat by erection of the hairs of its tail. In no case was any diminution in the diameter of the femoral artery observed (see Fig. 8). Identical results were obtained in both the rabbit and cat. The femoral artery was also stimulated directly with similar repetitive stimuli using electrodes held in contact with the artery on a rigid stand which prevented any movement likely to cause mechanical trauma. Upon no occasion did any change in diameter attributable to the electric stimulus occur. In these experiments the adventitia and perarterial tissue had been left in situ (Fig. 9).

These results indicate an absence of vasomotor fibers controlling the femoral arteries and similar experiments already mentioned upon other large vessels were in agreement.

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Fig. 7.—Rabbit anesthetized with Nembutal intraperitoneally (0.4 c.c. per kilogram) Adrenalin 0.5 c.c. intravenously at fourth signal. Order of records as in Fig. 1. This illustrates release of the ratchet mechanism of smooth muscle fibers which sometimes take up a new resting length with increase in blood pressure.

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fractory and further stimulation sometimes even produced localized fusiform dilatation similar to that described by Grant¹¹ in the rabbit's ear

Reflex Spasm of Large Arteries—Barnes and Trueta¹² working with rabbits, demonstrated a shrinkage of the arterial tree of the hind leg, on the side opposite to that on which a tourniquet had been in place for a time greater than an arbitrary period of four and a half hours. Injection of thorotrast into the abdominal aorta and radiography were used to outline the vessels of the hind legs. Trueta and associates¹³ used similar techniques and concluded that the distant vascular effects were due to nervous reflex mechanisms.

A series of tourniquet experiments was performed to examine the question of 'reflex' spasm more closely and some aspects of these have been alluded to previously under the heading of Methods. Records of the hind limb volumes, blood pressure, and right femoral artery diameter were begun about one half hour before release of the tourniquet which was applied as a convenient routine always to the left thigh. The diameter records and the records of limb volume and blood pressure on the snaked drum were afterward represented on paper in graphic form for each animal. Fig. 10 is an example of the typical pattern found in the animals with intact nervous system and Fig. 11 is an example of that found in animals in which bilateral lumbar sympathectomy (L_1 through S_2 or S_3) and local periarterial denervation of the right femoral artery had been performed. Shrinkage of the contralateral leg and of the femoral artery occurred in both groups as did a fall in blood pressure.

Table III summarizes the findings in animals with intact nervous systems and Table IV summarizes those in which the pathways had been interrupted.

COMMENTS ON TABLE III (TOURNIQUET EXPERIMENTS ON INTACT ANIMALS)

Anesthesia—Ambulal (sometimes with the addition of open ether) was used in the first 11 cases. Rapid deterioration was found to occur. This anesthesia was used because it was desired to repeat exactly the technique of Barnes and Trueta¹². A change was made to urethane in the later experiments in order to produce a more stable preparation and one which did not deteriorate so rapidly.

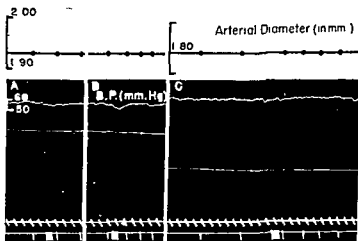
Regardless of the anesthetic used the relation between changes in contralateral leg volume and arterial diameter and changes in blood pressure remained constant.

Type of Tourniquet—With one exception all animals in which a wire tourniquet was used developed congestion of the limb which shrank after removal of the wire.

Contralateral Leg Volume—Shrinkage occurred in all cases but 3. In two of these three cases the blood pressure remained at a high level during the period of observation.

Right Femoral Artery Diameter—In all cases observed the right femoral artery diameter diminished during the period of observation, except in one case (animal 9).

MacWilliam¹⁰ found that stimulation with a strong galvanic current caused some contraction of pieces of ox artery in vitro. Using the same technique as before we applied galvanic stimuli to the femoral arteries of rabbits varying the strength from 4 to 11 volts. A marked local dilatation of the artery took place in the region of the electrodes. The dilatation took some one half to one minute to occur and subsided rapidly when the current was stopped. The degree of dilatation was larger with higher voltages but quite definite at 4 volts. It was repeated several times both on vessels with intact adventitia and on vessels with the adventitia removed. The response was the same in either case, suggesting that nervous factors played no part in the phenomenon.



Response to Mechanical Trauma—In contrast to the negative responses to nerve stimulation mechanical trauma easily produced spasm in the femoral artery of the rabbit or cat. Longitudinal stretching of a segment transverse stretching by means of fine dissecting forceps or pinching all produced it constantly. Rapid stretching was more effective than slow. A method which gave a constantly repeatable stimulus without damaging the vessel was that obtained by giving the vessel a sharp jerk at right angles with a length of cotton thread passed under it. This produced spasm of a segment of artery which came on in a slow and wormlike fashion; the lumen became occluded and pulsation disappeared. This spasm gradually wore off if the vessel was left undisturbed and by the end of one hour the vessel usually returned to its initial diameter. Similar behavior was observed in vessels denervated by removal of the adventitial coat. Immediately after relaxation further stretching was found to produce little or no response. The muscle fibers were re-

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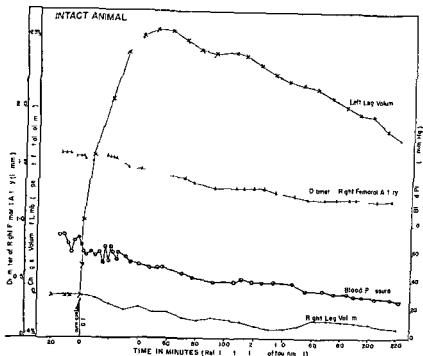


Fig. 10.—Rabbit anesthetized with urethane as in previous experiments. Nervous system intact. Rubber arterial tourniquet for five and one fourth hours left thigh. Decline in right femoral artery diameter, leg volume and blood pressure. (Animal 15 in Table III.)

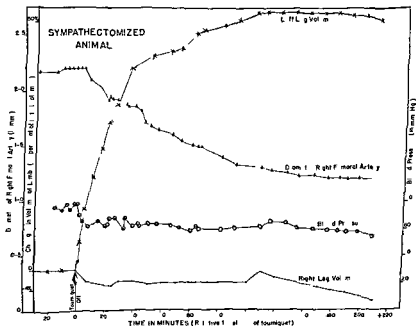


Fig. 11.—Rabbit anesthetized with urethane anesthesia as in previous experiments. Acutely sympathectomized hindlimbs. Rubber tourniquet released left thigh 1 hour on left thigh. Pattern of events is similar to intact animal (see Fig. 10) except that swelling of left leg is approximately twice as great. (Animal 10 in Table IV.)

TABLE III TOURNIQUE EXPERIMENTS (ANIMALS WITH INTACT NERVOUS SYSTEM)

NO	ANESTHESIA	TOURNIQUE		CLAMP 14134 VOL 1 MF		CHANGE IN DIAMETER OF RIGHT FEMORAL ARTERY (MM)			BLOOD PRESSURE (MM Hg) DURING PERIOD OF OBSERVATION			PERIOD OF OBSERVATION (MIN)
		TYPE	DURATION (HRS)	RIGHT	LEFT (TOURNIQUET SIDE)	INITIAL	FINAL	RANGE	INITIAL	FINAL	RANGE	
1	Nembutal and ether	Wire	7	Fall	fall	NR	NR	NR	78	70	8	48
2	Nembutal and ether	Wire	6½	Fall	Fall	NR	NR	NR	80	74	6	18
3	Nembutal and ether	Wire	6½	Fall	Fall	NR	NR	NR	38	44	6	65
4	Nembutal and ether	Wire	6½	Fall	Fall	NR	NR	NR	70	10	60	30
5	Nembutal and ether	Wire	5½	Fall	Fall	NR	NR	NR	63	45	0	32
6	Nembutal and ether	Wire	4½	Fall	Fall	NR	NR	NR	74	26	52	58
7	Nembutal and ether	Wire	3½	Fall	Rise	147	134	13	102	78	24	70
8	Nembutal and ether	Wire	7	Fall	Fall	200	159	41	73	24	49	100
9	Nembutal and ether	Wire	6	Fall	Fall	162	162	0	70	72	2	64
10	Nembutal and ether	Wire	3½	Fall	Fall	236	217	19	112	102	10	80
11	Nembutal and ether	Wire	7	Fall	Fall	141	140	1	NR	NR	NR	130
12	Urethane	Rubber	5½	Fall	Rise	141	114	27	72	60	12	115
13	Urethane	Rubber	5½	Fall	Rise	157	156	1	100	20	80	335
14	Urethane	Rubber	5½	Fall	Rise	137	113	24	64	38	26	207
15	Urethane	Rubber	5½	Fall	Rise	161	121	40	72	28	44	229

*Nit is abbreviation for not recorded
 †Rubber arterial tourniquet provided by Ramarch bandage

TABLE IV. SYMPATHETOMIZED OR DENERVATED ANIMALS

NO.	ANESTHESIA	TOXICITY		CHANGE IN LEFT VOLUME		CHANGE IN DIAMETER OF RIGHT FEMORAL ARTERY (MM.)			BLOOD PRESSURE (MM. HG) DURING PERIOD OF OBSERVATION			PERIOD OF OBSERVATION (MIN.)	OPNTRIO S YSTEM
		TYPE	DURATION (HR.)	RIGHT	LEFT (TORPENT QUET SHIP)	INITIAL	FINAL	RANGE	INITIAL	FINAL	RANGE		
1	Nonutal	Wire	5 1/4	Fall	Fall	1.3	1.0	30	64	30	34	145	ly left limb
2	Nonutal	Butter	6	Fall	Rise	1.66	1.10	47	85	46	39	96	ly left limb
3	Urethane	Butter	8	Rise	Rise	2.02	1.71	31	96	36	60	20	ly sympathet
4	Urethane	Butter	6 3/4	Fall	Rise	1.2	1.27	0.00	20	19	2	74	ly sympathet
5	Urethane	Butter	4	Nr	Nr	1.96	1.24	02	7	0	7	30	ly sympathet
6	Urethane	Butter	3	Fall	Rise	1.31	1.12	39	50	17	33	47	ly sympathet
7	Dial	Butter	3 1/4	Nr	Nr	1.33	1.20	13	70	26	44	96	ly sympathet
8	Urethane	Butter	2 1/2	Fall then rise	Rise	1.46	1.0	44	60	20	40	107	ly sympathet
9	Urethane	Butter	6 1/4	Fall	Fall	1.83	1.50	33	66	30	36	20	ly sympathet
10	Urethane	Butter	3	Fall	Rise	2.21	1.91	1.00	78	33	23	220	ly sympathet

Blood Pressure—The blood pressure fell during the period of observation in almost every case. Most of the animals with a rubber tourniquet showed an acceleration in the rate of fall just after removal of the tourniquet. This was not noticeable when a wire one was used presumably because the rabbit received a small transfusion from the distended veins when the wire was removed.

Period of Observation—The period of observation referred to in the last column was that time during which good blood pressure, leg volume and arterial diameter observations were made usually from a few minutes before the release of the tourniquet until the animal died or showed marked signs of deterioration although some of the earlier experiments were discontinued before this occurred.

COMMENTS ON TABLE IV

Cases 1 and 2 were animals in which all the somatic nerves of the left hind limbs had been divided at points where they left the pelvis one week before applying the tourniquet to the left thigh. The object was to see whether removal of these afferent pathways of a possible reflex arc would influence the shrinkage of limb volume and arterial diameter upon the opposite side. It did not do this in either animal.

In the remaining eight cases (animals 3 to 10) which had been sympathetomized it was found that

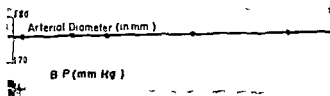
1 The contralateral limb volume shrank in four rose in one fluctuated in another and in two was not recorded owing to the poor condition of the animals.

Most showed minor fluctuations often in the opposite direction to the blood pressure which were not noticed in the intact animals. This is in line with the observations of Dale and Morrison² on sympathetomized and denervated limbs when investigating vasodilator action.

2 *Diameter of Right Femoral Artery* The diameter shrank in six out of eight cases following the trend of the blood pressure. Of the remaining two cases one had a very low blood pressure (20 mm.) at the start and the other animal died almost at once upon release of the tourniquet.

Blood Pressure A general downward trend occurred during the period of observation going parallel with the shrinkage of the contralateral femoral artery.

Summarizing the findings in the tourniquet experiments it is concluded that shrinkage of the artery and contralateral limb volume most certainly took place but that it occurred (with minor differences in leg volume change) in both the intact animals and in those which had denervated or sympathetomized limbs. The shrinkage of the artery went along with a falling blood pressure and in no case were abrupt changes observed such as might have been expected from the activation of a nervous reflex. Figs. 12 and 13 are portions excised from the records of an intact and a sympathetomized animal respectively showing the events which occurred on release of the tourniquet. No abrupt changes were evident such as might be expected were a nervous



as in preceding experiments.

reflex activated. The usual gradual downward trends in arterial diameter and contralateral leg volume occurred in both intact and sympathectomized animals as the blood pressure fell subsequently.

DISCUSSION

Spasm of the large arteries resulting from trauma has been recognized for many years and its clinical significance has been emphasized. Of great interest have been the reports of arterial spasm following trauma to the contralateral limb. Barnes and Trueta¹ have presented arteriographic evidence and suggested that this contralateral arterial spasm occurs as a result of a nervous reflex. Because of the clinical and physiologic implications it was thought desirable to reinvestigate the problem of "reflex spasm" in the large arteries.

On the basis of available evidence (Moore and Moore¹⁶ Moore and Singleton,¹⁷ and Simeone and Watkins¹⁸) reflex effects from irritation of large arteries would not be expected. The radiographic data obtained by Barnes and Trueta were recorded some time after release of the tourniquet. During this lapse of time possible changes in the arterial blood pressure of the animals which per se might have affected the caliber of the arteries, were not recorded. They used light nembutal anesthesia supplemented with ether when needed. The possible effects of supplementary anesthesia itself on arterial caliber were not controlled. The technique of arteriography involved celiotomy and aortic puncture. The possible effects of these procedures themselves upon an animal which is deteriorating after hours of anesthesia require control.

The results of experiments recorded in this report indicate that changes in the diameter of the femoral artery do occur after release of the tourniquet (Figs. 10 and 11). However it appears that these changes are purely passive. In the first place the diameter of the artery varies in direct proportion with the systemic arterial blood pressure. Rises in blood pressure obtained by whatever means are attended by an increase in the diameter of the femoral artery (Figs. 1 and 4). Falls in systemic blood pressure by whatever methods produced are attended by a shrinkage of the femoral artery (Figs. 2, 5 and 6). Furthermore these changes in diameter of the femoral artery occur regardless of whether the systemic nerves or the sympathetic nerves to the limb are intact or ablated (Tables III and IV, Figs. 10 and 11). Indeed Fig. 13 shows that in this particular rabbit the slight fall in blood pressure associated with release of the tourniquet was attended by a shrinkage in the sympathectomized paw (upper plethysmographic record) without any shrinkage in the normally innervated paw (lower plethysmographic record). Had a reflex been produced by removal of the tourniquet one would have expected a greater change in the normally innervated limb than in the sympathectomized limb.

The experiments reported in this paper have further tested the concept of reflex spasm in large arteries by tests on the efferent segments of the possible reflex arc. Stimulation of the decentralized lumbar ganglionated trunk produced plethysmographic shrinkage of the paw without shrinkage of the

femoral artery (Fig 8) Direct electric stimulation of the femoral artery and its adventitia produced no change in the caliber of this vessel (Fig 9) If the femoral artery were a part of a reflex arc one would expect that these procedures would affect its caliber These observations are in accord with the findings of MacWilliam¹⁰ on excised arterial segments and with those of Rosenblueth and Cannon¹¹ on the denervated intestinal membrane

That the criticism of the administration of additional anesthetic agent during the experiment is reasonable is demonstrated by Figs 5 and 6, which indicate that both nembutal and ether may themselves produce a change in the diameter of the femoral artery as a result of their effect on the systemic blood pressure

The experiments reported here suggest that while the femoral artery is not under the direct control of the nervous system it can alter its size on a myogenic basis (stretch) and as a passive reflection of the systemic blood pressure

A curious phenomenon was observed during the course of these experiments Following positive stretching of the artery by a rise in systemic blood pressure induced by adrenalin the wall of the artery suddenly relaxed and assumed a new resting position (Figs 3 and 7), reminiscent of the mollusc adductor with its "ratchet device" The behavior of the arterial diameter subsequently followed the various stimuli in the usual manner but from its new resting level

CONCLUSIONS

1 Local segmental spasm in the large arteries can be produced by mechanical trauma irrespective of the presence of the adventitia and possible nerve supply

2 Electric stimulation of the sympathetic nerve supply to the limb or of the artery and its adventitia directly has failed to reveal evidence of nervous motor control of the large arteries

3 After release of a tourniquet applied to the thigh for two and one half to seven hours there is a demonstrable shrinkage of the contralateral femoral artery

4 The shrinkage of the femoral artery develops slowly and not abruptly after removal of the tourniquet from the contralateral thigh

5 The observed shrinkage of the femoral artery is a consequence of the gradual fall in blood pressure and not a result of reflex activity

6 The caliber of the large arteries follows passively the systemic blood pressure it increases with rises in blood pressure and decreases with falls in blood pressure howsoever these are produced

REFERENCES

- 1 Kroh, F. Kriegschirurgische Erfahrungen einer Sanitätskompagnie Beitr z klin. Chir. 57 21, 29b 1915
- 2 Froh
- 3 Kutt

- 4 Sencert I Le traitement des plaies vasculaires a l'avant Lyon chir 14 640 694 1914
- 5 Kuttner H and Baruch M Beitrage zur Chirurgie der grossen Blutgefasse
IV Der traumatisch segmentare Gefasskrampf Beitr z klin Chir 120 124, 1920
- 6 Cohen S M Traumatic Arterial Spasm Guy & Hosp Rep 90 201 216 1940 1941
- 7 DeBakey, M F, and Simeone F A Battle Injuries of the Arteries in World War II Ann Surg 123 534 579 1946
- 8 Griffiths P I Observations on Fractures and Arterial Spasm, Brit J Surg, 28 239 240 1940
- 9 Lister J An Address on the Influence of Position Upon Local Circulation Brit M J 1 923 926 1849
- 10 MacWilliam J A On the Properties of the Arterial and Venous Walls Proc Roy Soc 70 101 103 1902
- 11 Crant R T Observations on Local Arterial Reactions in the Rabbit & Far Heart 15 251 260 1930
- 12 Barnes J M and Trueta J Arterial Spasm An Experimental Study Brit J Surg, 30 479 1942
- 13 Trueta J Barclay A F Daniel R M Franklin K J and Irichard M M I Studies of the Renal Circulation Oxford 1947 Blackwell Scientific Publications Springfield Ill 194 Charles C Thomas Publisher
- 14 Hunter J Works of edited by Palmer vol 3 London 1837 Longman Rees Orme
- 15 Dole ion of Reflex Activation of
- 16 Moor Sensibility of Arteries Am
- 17 Moor Studies on the Pain Sensibility of Arteries
- 18
- 19 ion of Denervated

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REFERENCES

- 1 Kroh, F. Kriegschirurgische Erfahrungen einer Sanitätskompanie Beitr. z. klin. Chir. 97 342 396 1917
- 2 Kroh
- 3 Kuntz

parietal pleura and dividing and ligating four to six intercostal arteries. The animal was then heparinized using 10 mg per kilogram of body weight. Non-crushing clamps were applied proximally and distally and the aorta was partially divided. Glass cannulas approximately the diameter of the aorta were inserted and secured with heavy silk ligatures. The glass cannulas were connected to the bubble meter by rubber tubing the entire system having been filled with physiological saline solution. When the clamps were removed all of the blood flowing through the descending aortic arch passed through the bubble meter (Figs 1 and 2). Following removal of the clamps the blood pressure usually dropped from 20 to 60 mm of mercury. After waiting for the blood pressure to return to its maximum level and become stabilized recordings were taken of the rate of blood flow resulting from spontaneous cardiac activity. The heart was then stopped by the rapid intravenous injection of 10.0 to 15.0 cc

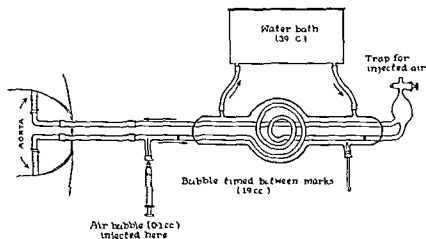


Fig 1—A diagram of the bubble meter in a dog's thoracic aorta. All of the blood flowing through the descending thoracic aorta passed through the bubble meter. The rate of blood flow was determined by measuring the time required for an air bubble to pass between the measuring marks on the inflow arm of the bubble meter.

of a saturated solution of magnesium sulfate and cardiac massage was begun at a rate of 60 times per minute. The ether valve in the positive pressure apparatus was shut off and room air was used for ventilation of the lungs during the remainder of the experiment. Blood flow through the bubble meter was recorded at frequent intervals with varying rates of cardiac compression and relaxation and of intravenous administration of blood and physiologic saline solution. In most instances the experiment was terminated within forty five minutes after stopping the heart because unless adequate blood was given there was significant depletion of the blood volume due to oozing from raw surfaces.

In experiments measuring the blood flow through the carotid artery the left side of the chest was opened and the animal was heparinized before inserting cannulas connected to the bubble meter into the carotid artery. After recordings of the carotid blood flow due to spontaneous cardiac activity were taken

AN EXPERIMENTAL STUDY OF CARDIAC MASSAGE

JULIAN JOHNSON, M.D., AND CHARLES K. KIRBY, M.D., PHILADELPHIA, PA.

(From the Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania)

DURING the treatment of patients with cardiac arrest some of whom were recently reported upon¹ the authors have been uncertain about the rate at which the heart should be compressed. A review of the literature reveals a difference of opinion. Bost, in analyzing the seventy-five cases of attempted cardiac resuscitation recorded before 1923, stated that it was 'pretty well agreed that gentle compression of the heart should be carried out at about half the normal rate to allow the heart to fill well'. Lee and Downs² added twenty-four cases to those collected by Bost and recommended massage at a rate of '20 times a minute' for when it resumes its beat it will start slowly. Barber and Madden³ reviewed the world literature in 1944 and suggested a rate approximately one half the normal or 40 or 50 times per minute. They stated that a slow rate allowed a more complete filling of the heart with an increase in the stroke and minute volume output. No data were presented in support of this statement. Ruzicka and Nicholson⁴ considered 40 times a minute to be the optimal rate while Crafoord⁵ reported that he used about the same rhythm as the normal heartbeat.

Since there have been no experimental studies to our knowledge of the relationship between the rate of manual cardiac compression and the artificial circulation produced the answer to this and to certain related problems were sought in the experiments herein described. The rate of blood flow was considered to be the best criterion of the efficiency of cardiac massage.

EXPERIMENT METHOD

The instrument used to measure blood flow was the bubble meter of Dumble and Schmidt.⁶ This instrument has been found to be accurate and dependable with no appreciable resistance to the blood flow even of small arteries (coronary) and no marked deviations resulting from changes in blood viscosity.⁷

Mongrel dogs averaging about 100 kilograms in weight were anesthetized with ether. An intratracheal tube was inserted and connected to an intermittent positive pressure apparatus delivering an air-ether mixture. The femoral vein was cannulated for the administration of intravenous fluids and the mean arterial pressure was recorded through a cannula in a carotid or femoral artery.

In experiments measuring the blood flow through the thoracic aorta the left chest was opened through the fifth intercostal space and in some animals the adjacent costal cartilages were divided in addition to increase exposure. Hemostasis was made as complete as possible to minimize oozing following heparinization. The aorta distal to the subclavian artery was mobilized by reflecting the

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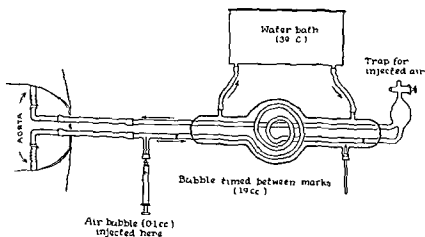


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TABLE I EFFECT OF THE RATE OF CARDIAC COMPRESSION ON BLOOD FLOW
(CUBIC CENTIMETER PER MINUTE)

EXPERIMENT	30 PER MIN	60 PER MIN	120 PER MIN
Thoracic aorta			
132	109.6	193.2	250.5
133	151.1	262.1	278.3
142	20.3	34.6	408.6
143		222.6	322.1
144	87.6	143.1	212.64
Carotid artery			
130	20.1	37.0	42.5
139	16.9	31.5	43.8
151	15.1	28.5	33.2

TABLE II BLOOD FLOW DUE TO SPONTANEOUS HEARTBEAT AND CARDIAC COMPRESSION (CHEST OPEN, AORTA CANNULATED)

EXPERIMENT	SPONTANEOUS CARDIAC ACTIVITY (CC PER MIN)	CARDIAC MASSAGE (CC PER MIN)		B.P.
		60 PER MIN	120 PER MIN	
132	43.8	17.0	25.6	-
134	40.5	28.6		-
138	44.4	173.2	250.5	90
141	65.4	26.0	179.7	70
142	25.8	324.6	408.6	30
143	27.0	22.4	322.0	70
144	40.6	145.1	212.6	90

and 120 times per minute. In two instances (Experiments 142-143) it was possible to move more blood by cardiac compression than was moved by the spontaneously beating heart. In both of these experiments the systolic pressure had dropped to 30 mm Hg following cannulization of the aorta and this undoubtedly accounted for the relatively slow rate of blood flow before the heart was stopped. In all other instances the rate of blood flow during cardiac massage was less than before the heart was stopped. In no instance, however, was the rate of flow due to cardiac compression at 120 per minute less than one half of that resulting from the normal spontaneous heartbeat.

The Effect on the Carotid Circulation of Occlusion of the Thoracic Aorta During Cardiac Massage—Since cerebral cortical tissue is believed to be the most sensitive to anoxic damage during cardiac arrest, it was of interest to determine whether cerebral blood flow could be increased by occlusion of the thoracic aorta during cardiac massage. Wiggers suggested this maneuver to increase coronary artery flow, but to our knowledge it has not been used or studied as a procedure to increase cerebral blood flow and oxygenation during cardiac resuscitation. Table III shows the marked increase in carotid blood flow in three experiments.

TABLE III EFFECT ON CAROTID BLOOD FLOW OF OCCLUSION OF THE THORACIC AORTA DURING CARDIAC MASSAGE

EXPERIMENT NUMBER	AORTA PATENT (CC PER MIN)	AORTA OCCLUDED (CC PER MIN)
130	71.2	54.5
150	26.4	55.1
151	27.0	51.7

the heart was stopped as before and cardiac massage was begun at the rate of 60 times per minute. Frequent recordings of the carotid blood flow were then taken with and without the thoracic aorta occluded by a noncrushing clamp with varying rates of cardiac compression, and with varying rates of blood and physiologic saline solution injected intravenously.

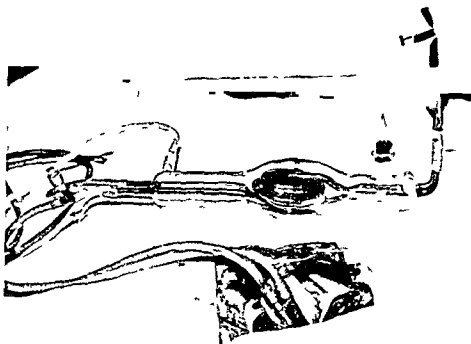


Fig. —A photograph taken during one of the experiments. The cannula in the thoracic aorta as seen in the chest incision. The heart is beating spontaneously and blood is flowing through the bubble meter.

RESULTS

Effect of the Rate of Cardiac Compression on Blood Flow—In Table I the rate of blood flow in the thoracic aorta (six experiments) and in the carotid artery (three experiments) is shown at different rates of cardiac compression. The figures shown are the average of many consecutive recordings at 30, 60 and 120 compressions per minute. A smaller number of recordings at 45 and 90 times a minute fell between the rates of flow at 30 to 60 and 60 to 120 times per minute. Up to a rate of 120 per minute the rate of flow appeared to increase progressively as the rate of compression was increased. This was true when the blood volume had been depleted and the heart felt relatively empty as well as when venous return was adequate and the heart felt full in the operator's hand.

Comparison of Blood Flow Due to Spontaneous Heartbeat and to Cardiac Massage—In Table II the rate of blood flow in the thoracic aorta is shown with (a) spontaneous heartbeat with an open chest and (b) cardiac massage at 60

one half the rate of 760 c.c. per minute produced by holding the heart and compressing it between the fingers and thumb

COMMENT

The use of the bubble meter, an accurate instrument for measuring blood flow, afforded an opportunity to study certain details of the technique of cardiac massage. The first attempts of all who tried the procedure were relatively ineffectual. Practice was required in order to obtain maximal rates of blood flow. There were several minor variations in the technique of holding the heart which were considered preferable by different observers, but the most effective maneuver appeared to be compression between one or more digits in front and one or more digits behind the heart. The human heart, in our experience, may be too large to hold effectively in one hand and it may be preferable to apply compression between two hands. Compression of the dog's heart against the anterior chest wall was relatively unsuccessful and massage through the intact diaphragm proved to be a poor method. Although some circulation has been shown by radioactive tracer techniques to result from artificial ventilation of the lungs,¹⁹ it was not sufficient to be detectable with the bubble meter in our experiments.

The optimum rate at which the heart should be compressed appears to be the fastest rate at which the heart can be compressed—at least up to 120 per minute. At rates approaching 120 per minute fatigue of the operator becomes a limiting factor. Whereas a rate of 60 per minute could be maintained for twenty-five to thirty minutes without great discomfort, a rate of 120 per minute could not be continued for more than a few minutes because of cramping pain in the forearm. In patients requiring cardiac massage for more than a few minutes it would seem advisable therefore to provide a substitute for the operator in order to maintain a rapid rate.

The increase in carotid blood flow which followed occlusion of the thoracic aorta during cardiac massage in dogs is regarded as evidence in favor of applying a noncrushing clamp or manual pressure at least intermittently to the thoracic aorta of patients during cardiac resuscitation. The additional oxygenation provided to the brain and myocardium at the expense of some oxygen deprivation of the more resistant organs below the point of aortic occlusion is probably warranted during the brief period in which the issue of restoration of the heartbeat is settled.

The importance of maintaining an adequate blood volume and supporting the venous return to the heart by the rapid intravenous administration of blood or physiologic saline solution became evident in these experiments. In the excitement and confusion which may accompany attempts at cardiac resuscitation in patients intravenous therapy must not be neglected.

CONCLUSIONS

1. The technique of cardiac massage was studied in dogs using the bubble meter of Dumke and Schmidt to measure the rate of blood flow.

It is evident that a considerably larger volume of blood was delivered to the cerebral tissues during cardiac compression when a noncrushing clamp was applied to the thoracic aorta.

The Effect of the Rapid Administration of Intravenous Fluids on the Rate of Blood During Cardiac Massage—After fifteen to twenty minutes of cardiac massage the blood flow in the thoracic aorta and carotid artery decreased significantly in most experiments. When this occurred, the heart felt empty and there appeared to be inadequate diastolic filling. Although intravenous saline solution had been continuously administered at a moderate rate, oozing from the incision, due to hepatization was rapid. The poor venous return to the heart appeared to be due to a decreased blood volume. When saline solution or blood was injected rapidly (500 cc per minute) the heart could be felt to fill in the operator's hand and the blood flow returned to or exceeded that obtained soon after the heart was stopped. In Experiment 132 for example the blood flow through the thoracic aorta soon after the heart was stopped was 172 cc per minute. Ten minutes later when the heart felt empty, the rate of flow had fallen to 81.6 cc per minute. After 600 cc of blood were rapidly given (150 cc per minute), the blood flow increased to 202.8 cc per minute.

Because of the generalized vascular and capillary dilatation which follows cardiac arrest and the low systolic pressure produced by cardiac compression (40 mm Hg), the venous return to the heart is presumably poor during attempted cardiac resuscitation. The rapid intravenous administration of blood might increase the venous return sufficiently to provide an increased increment in the cardiac output of oxygenated blood to the brain and other vital organs. This was done in Experiment 134. Soon after the heart was stopped, before there had been a significant depletion of the blood volume 500 cc of blood were given intravenously in three minutes. The rate of blood flow in the thoracic aorta increased from 282.6 to 344.6 cc per minute.

Other Observations—In Experiment 157 in which the bubble meter was connected to the abdominal aorta retroperitoneally, three other points were studied as follows:

1 Does artificial ventilation of the lungs with intermittent intratracheal positive pressure produce significant circulation of blood? Immediately after the heart was stopped an air bubble was introduced. It did not move. Any movement of blood which may result from artificial ventilation as demonstrated by Thompson, Quimby and Smith¹⁰ with a radioactive tracer technique was not apparent in the bubble meter.

2 Is cardiac massage through the intact diaphragm effective? An upper midline incision was made and the operator attempted to compress the heart without dividing the diaphragm. The heart could not be grasped, but blood flow at a slow rate (17.0 cc per minute) resulted from rhythmic thrusts at a rate of 60 per minute against the apex of the heart.

3 Is compression of the heart against the anterior chest wall an effective method of cardiac massage? The chest was opened and this maneuver at a rate of 60 per minute resulted in a blood flow of 41.6 cc per minute which was about

AN EVALUATION OF ELECTROGASTROGRAPHY IN THE DIAGNOSIS OF GASTRIC CANCER

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THE electrogastrogram, as performed in this series, is a chart on which the potential difference between the gastric mucosa and the skin is plotted against time for thirty minutes. After the first fifteen minutes the subject drinks 200 cc. of whole milk. The clinical application of the measurement of gastric potential was made by Goodman¹ in 1942. The physiologic experiments on which it is based go back at least fifty-nine years to the work of Biederman, Böhlen² and others.

In this paper the method will be described first. It has been modified slightly from that of Goodman.¹ Next the results in patients will be presented. The results have been analyzed in two ways, first by comparing the interpretation of the electrogastrogram recorded preoperatively with the pathologic findings at operation and second by setting up certain rigid wholly objective criteria by which all records could be classified as (1) undiagnosable (2) indicative of a benign status and (3) indicative of malignancy. Finally a few observations made to throw light on the relation of gastric potential to gastric hydrochloric acid secretion will be reported and the recent literature on this subject alluded to.

Fig. 1 shows the test in progress. The Levine tube to the stomach is filled with 0.1 N hydrochloric acid which permeates a sponge rubber plug in the lower end of the tube and at the outer end connects through a calomel half cell to a high resistance recording potentiometer. The lower end of the tube is placed under fluoroscopic control against the gastric wall opposite the esophageal opening. The other electrode is filled with 0.1 N sodium chloride and placed against a scarified area on the skin surface of the arm. If these two electrodes are brought into direct contact through a potassium chloride bridge no potential results.

After the gastric tube is placed the patient lies down. The leads are connected to the potentiometer and a record begun. The normal stomach is electrically negative to the skin by a potential difference of 20 to 80 millivolts. After a base line has been obtained the subject drinks 200 cc. of milk and the record is continued an additional fifteen minutes. The test should be run after a fast of at least twelve hours. Typical responses are shown in Fig. 2. The normal stomach has a smooth even base line between 20 and 80 millivolts. The response to milk at the fifteen minute mark is prompt and smooth gradually rising and then falling to the previous base line. On the

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occurrence of a gastric lesion, such as gastric ulcer, the base line becomes more uneven. The response to the ingestion of milk in benign lesions is in most cases immediate and prolonged. The response to milk may itself be very uneven.

In patients with duodenal ulcers with simultaneous gastric lesions the curve tends to resemble the curve of a gastric ulcer. In patients with gastric carcinoma, the base line is moderately to extremely uneven; the response to milk becomes atypical in 87 per cent of the cases. The response either does not take place in less than sixty seconds, or never gets greater than 3 mv, or does not last as long as three minutes.

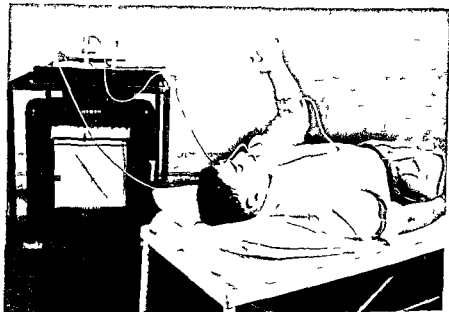


Fig. 1—The technique of electrogastragraphy

RESULTS

One hundred six patients were tested, 130 tests being run. Forty-two additional experiments were run on subjects presumed to be normal. In these only twenty tests in twelve individuals were run with milk. All of these gave normal responses. Of the 106 patients, seventy-six were subsequently operated upon and a pathologic diagnosis obtained. The other thirty patients were not operated upon but accumulated strong clinical evidence indicated that no malignant lesion of the stomach existed. So far there has been no reason to reverse the diagnosis in any of these thirty patients. Comparison of the immediate electrogastragraphic diagnosis with the final diagnosis thus obtained showed that of those subjects who had no malignancy the test was interpreted as indicative of a benign status in sixty-two of seventy-one patients or 87 per cent.

TYPICAL ELECTROGASTROGRAMS

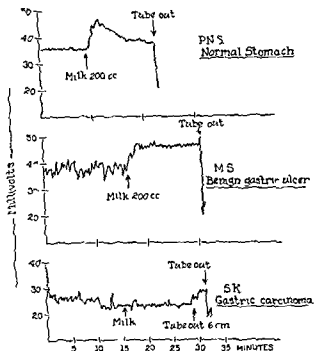


Fig. 2—The records illustrate typical curves obtained from a subject with a normal stomach, a patient with gastric ulcer, and a patient with gastric carcinoma. The occurrence of a gastric ulcer usually masks the basic line more unevenly while the presence of gastric carcinoma shows the response to the milk meal in marked contrast.

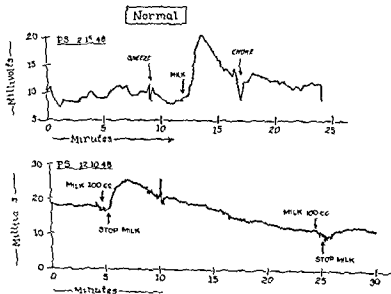


Fig. 3—Two normal curves are shown. The top curve is a record obtained with a hand portable potentiometer. The bottom record is from the same patient using the Splanmax recorder (an automatic recording potentiometer leads and Northrup Co. Philadelphia, Pa.)

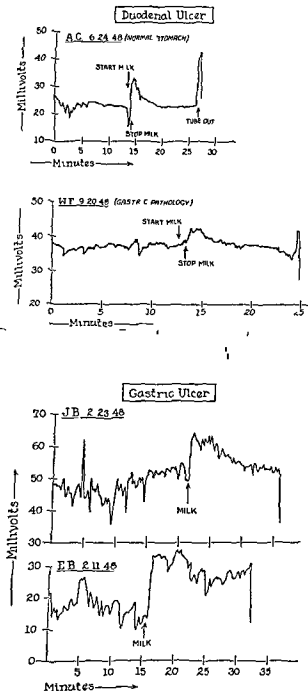


Fig. 5.—The presence of gastric ulcer often causes an extremely uneven base line. The response to milk is significant in the great majority of cases. The base line usually continues uneven after ingestion of milk.

In the thirty five patients who proved to have gastric cancer, the test was interpreted preoperatively as indicating gastric malignancy in twenty nine, or 83 per cent. Representative electrogastrograms are shown in Figs 3 to 6. The normal subject has a smooth base line and a normal, smooth response to milk. The patients with duodenal ulcers have a smooth base line and a normal but more striking response to milk if there is no concomitant gastric lesion. With gastric disease, the base line tends to resemble that of gastric ulcer.

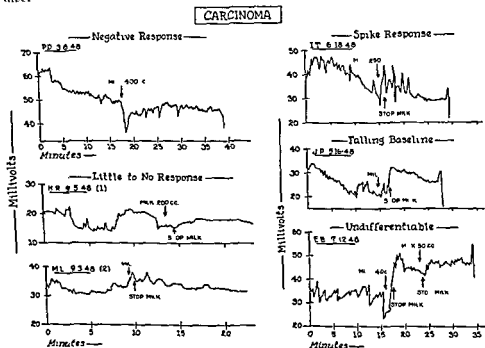


Fig. 6—Six curves in patients with gastric carcinoma. The curves are classified according to the type of response to milk. Type 1 demonstrates a negative response to milk.

Patients with gastric ulcers have an uneven base line of 18 to 60 mv with an uneven but significant response to milk usually greater than in the case of the normal stomach.

The occurrence of gastric malignancy makes the base line very uneven in general. The response to milk in the patient with gastric carcinoma (Fig. 6) has been divided into six groups.

I realize that the appearance of the patient or chance information about other clinical findings might influence the interpretation of the less typical records; the records were later reviewed in accordance with the criteria shown in Table I.

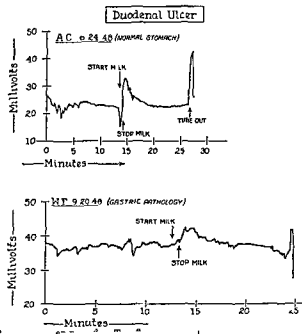


Fig. 4—D

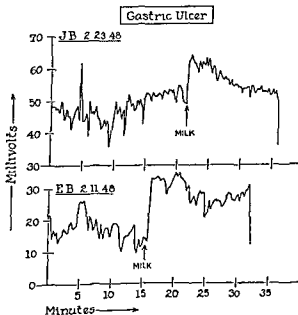


Fig. 5—The presence of gastric ulcer often causes an extremely uneven base line. The response to milk is significant in the great majority of cases. The base line usually continues uneven after ingestion of milk.

As Tables II and III show, histamine hypodermically gives a fall in potential and atropine, a rise in potential. The response to histamine might suggest that increased secretion of hydrochloric acid leads to a decrease in potential in an external circuit. Likewise the response to atropine might suggest that a rise in potential accompanies the inhibition of gastric acid secretion by this drug. Thus a rise in potential might indicate an inhibitory phenomenon.

TABLE II ANALYSIS OF RESPONSE OF GASTRIC POTENTIAL TO ALCOHOL HISTAMINE ATROPINE (AND DERIVATIVES)

TEST	METHOD ADMINISTERED	NUMBER OF TESTS	LEAST EST. RESPONSE (MV)	GREATEST EST. RESPONSE (MV)	MEAN RESPONSE (MV)	LONGEST DURATION (MIN)	SHORTEST DURATION (MIN)	MEAN DURATION (MIN)
1 cc whisky 400 cc	P.O.	3	-3	-30	-19	1	15	27
Histamine 0.3 mg	S.C.	5	-4	-13	-9	1+	15	26
Atropine 0.04 mg	S.C.							
Dibutylolone 100 cc (Atropine like drug)	S.C.	4	+23	+33	+24.75	1+	20++	30+
Urecholine 100 mg	S.C.	1			-9			30++

Following previous ingestion of alcohol until could not stand into final contractions and 1 mg r

TABLE III THE RESPONSE OF GASTRIC POTENTIAL TO VARIOUS PHARMACOLOGIC AGENTS

TEST	SUBJECT	RESPONSE (MV)	DURATION
1 cc alcohol 400 cc	I N 4	-3	15 min
1 cc alcohol 400 cc	I N 4	-8	1 hr +
1 cc whisky 400 cc	I N 4	-30	20 min +
1 cc whisky 100 cc	I P	23	17 min +
alcohol 400 cc	I N 4	-20	23 min +
Histamine 0.3 mg (S.C.)	I N 4	-4	15 min
Histamine 0.3 mg (S.C.)	I N 4	-6	60 min +
Histamine 0.4 mg (S.C.)	I N 4	-12	15 min
Histamine 0.3 mg (S.C.)	I P	-10	20 min
Histamine 0.3 mg (S.C.)	I N 4	-13	20 min
Atropine 0.1 mg (S.C.)	I N 4	+33	45 min +
Atropine 0.4 mg (S.C.)	I P	+14	25 min +
Atropine 0.8 mg (S.C.)	I N 4	+27	35 min +
Dibutylolone 500 mg (S.C.)	I N 4	+21	60 min +
Urecholine 100 mg (S.C.)	I N 4	-9	30 min +

The third hypothesis that the changes are due to action potentials associated with the contraction of the gastric muscles is refuted by the fact that urecholine which stimulates gastric contractions did not increase the irregularity of the electrogastrogram. Furthermore gastric potential is relatively constant in fasting normal stomachs until stimulated by milk whereas gastric muscle action potentials are a periodic phenomenon. The same potential level is obtained in stomach mucosae from which the muscularis has been dissected away (Kehm⁶ and Sawyer and Rhoads⁷). Davies and co-workers⁸ were able to measure the same potential level in free isolated frog gastric mucosa.

The theory that the action current of skeletal muscle produced the changes was refuted by moving the arm to which the skin electrode was attached and

TABLE I AN OBJECTIVE METHOD FOR THE INTERPRETATION OF ELECTROGASTROGRAMS

<i>Group I</i> —Not interpretable	
(a) Slope of base line change more than 8 mv in 15 min.	
<i>Group II</i> —Benign lesions	
(a) Rise in potential of at least 3 mv	
(b) Rise must start within 1 min of ingestion of milk and last at least 3 min before potential returns to previous level	
<i>Group III</i> —Malignant lesions	
(a) All other curves	

On this basis, it was necessary to discard nine tests 85 per cent of the records, as uninterpretable. Of those remaining the percentage of correct diagnoses in the thirty cases of gastric cancer with interpretable records was 87 per cent and the percentage of correct diagnoses of the absence of gastric cancer in those sixty seven with interpretable electrogastrograms was 88 per cent. While the series is not large, we believe that it is large enough to indicate that gastric cancer does usually alter the electrical response of the fasting human stomach to the ingestion of milk and to indicate that the relation is not invariably present and hence probably not a direct relationship but one which may perhaps be mediated through other changes which occur frequently but not constantly with gastric cancer.

Initially we considered five possible ways in which the potential difference might be altered by the ingestion of milk

- 1 Chemical reaction of the milk with the gastric contents
- 2 Chemical reaction of subsequent gastric secretions with the milk
- 3 Action currents due to muscular contractions in the stomach
- 4 Action currents due to muscular contractions elsewhere
- 5 Electrochemical changes in the cells associated with their secretory activity

Goodman¹ tested the first hypothesis by adding the milk to gastric juice *in vitro*. The typical changes did not occur. We have repeated this work and found that, while the measured potential will change on the addition of milk to gastric juice, it will in no way change as significantly as did the potential change *in vivo*. The curve type *in vitro* is not similar to that *in vivo*, the addition of milk changes the potential difference measured in a stepwise manner as would be expected if pH were increased in steps. The potential — — — — — returns to its previous level as it does *in vivo*. The variability in re-

There are several bits of evidence against the second hypothesis. Several the changes are due to subsequent secretion into the milk meal). Several authors⁴ have shown that hydrochloric acid is secreted at an almost constant concentration with a pH near 1.0. Hollander⁴ and Lifson, Varco and Visscher⁵ have shown that the ionic concentration of gastric secretion is remarkably constant. Furthermore we have observed that patients with achlorhydria may give a normal electrical response which would be indicative evidence against both the first hypotheses.

of this energy is utilized in the formation of hydrochloric acid which, it is postulated takes place by the dissociation of H_2O into H^+ and OH^- ions in the oxyntic cells. As the secretion of hydrochloric acid occurs less energy is available as external electrical energy. The reverse is true when atropine is used.

SUMMARY

A series of 150 electrogastrograms has been analyzed. Of these, 130 were run on 106 patients and twenty on twelve normal subjects. The method employed which is a modification of that reported by Goodman has been described. The origin of the gastric potential and its relation to gastric secretion have been considered in the light of certain experimental observations and in the light of recent reports in the physiologic literature. Two ways of analyzing the results in patients were employed. Of the more objective of the two 85 per cent of the records had to be discarded but in the remainder the test was correct in 87 per cent of the patients with malignant gastric lesions and in 88 per cent of the patients who did not have malignant gastric lesions.

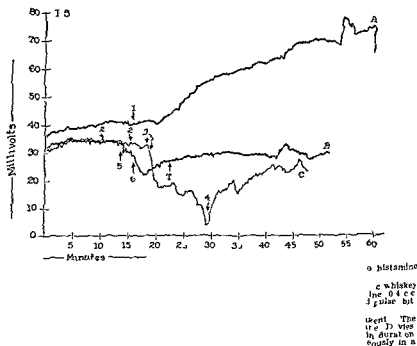
Thus our experience confirms that of Goodman and while the test is not to be relied upon for definitive diagnosis of gastric malignancy we believe it may prove of value as a screening test in cancer detection for it should be less expensive than gastrointestinal x-ray examinations as now carried out.

REFERENCES

- 1 Goodman F N Improved Method of Measuring Potential Difference Across the Human Gastric Membranes and Its Clinical Significance Surg, Gynec & Obst 75 593 1942
- 2 Biederman W (translation by Wells F A) Electrophysiology London and New York 1896 Macmillan & Co Ltd
- 3 Nohlen E Ueber die Electromotorischen Wirkungen der Magenschleimhaut, Arch f d ges Physiol 57 91 1894
- 4 Hollander F The Composition of Gastric Juice as a Function of Its Activity J Biol Chem 104 33 1934
- 5 Lifson N Varro R L and Vischer M B The Relationship Between the Total Osmotic Pressure of Gastric Juice and Its Acidity Gastroenterology 1 764 1943
- 6 Rehm W S Evidence That the Major Portion of Gastric Potential Originates Between Submucosa and Mucosa Am J Physiol 147 69 1946
- 7 Sawyer P N and Phoad J F Unpublished data
- 8 Crane F F Davies R F and Longmuir N M Relation Between Hydrochloric Acid Secretion and Electrical Phenomena in Frog Gastric Mucosa Biochem J 43 3-1 1949
- 9 Rehm W S Effect of Histamine and Hydrochloric Acid on Gastric Secretion and Potential, Am J Physiol 141 537 1944
- 10 Crane F F Davies R F and Longmuir N M The Effect of Electrical Current on Hydrochloric Acid Secretion by Isolated Frog Gastric Mucosa Biochem J 43 337 1948

by running in place. Neither of these activities materially affected the gastric potential as recorded.

By a process of exclusion one is led toward the belief that the potential results from metabolic activity of the secretory cells. Rehm⁸ brought forth evidence in the dog which we have confirmed, indicating that the potential arose in gastric mucosa from which all muscle layers had been removed except the muscularis mucosae, which cannot readily be separated. Fig. 7 shows the electrical responses of the human stomach to histamine, atropine and ethanol. The effect of histamine on the human stomach is similar to that observed in the dog by Rehm⁸ and in the isolated frog stomach by Crane, Davies and Longmuir.^{9, 10} This leads us to believe that we are measuring the same phenomenon.



All of these workers have tentatively shown that the energy necessary for the increased production of hydrochloric acid under histamine stimulation corresponds to the decrease in electrical energy in an external circuit which occurs with this drug. The latter authors showed that oxygen deprivation stopped hydrochloric acid secretion and reduced the potential to zero. Both could be restored by oxygenation. It is therefore postulated that the acid-secreting oxyntic cells develop energy by combustion of foodstuffs which is evident as external electrical energy on the one hand or utilized in formation of acid on the other. When secretion is stimulated by histamine more

of this energy is utilized in the formation of hydrochloric acid which, it is postulated takes place by the dissociation of H₂O into H⁺ and OH⁻ ions in the oxyntic cells. As the secretion of hydrochloric acid occurs less energy is available as external electrical energy. The reverse is true when atropine is used.

SUMMARY

A series of 150 electrogastragrams has been analyzed. Of these 130 were run on 106 patients and twenty on twelve normal subjects. The method employed which is a modification of that reported by Goodman has been described. The origin of the gastric potential and its relation to gastric secretion have been considered in the light of certain experimental observations and in the light of recent reports in the physiologic literature. Two ways of analyzing the results in patients were employed. By the more objective of the two 85 per cent of the records had to be discarded but in the remainder the test was correct in 87 per cent of the patients with malignant gastric lesions and in 88 per cent of the patients who did not have malignant gastric lesions.

Thus our experience confirms that of Goodman and while the test is not to be relied upon for definitive diagnosis of gastric malignancy we believe it may prove of value as a screening test in cancer detection for it should be less expensive than gastrointestinal x-ray examinations as now carried out.

REFERENCES

- 1 Goodman L N Improved Method of Measuring Potential Difference Across the Human Gastric Membranes and Its Clinical Significance Surg Gynec & Obst 75 43 1942
- 2 Bielerman W (translation by Welby F A) Electrophysiology London and New York 1930
- 3 Bohle f Wirkungen der Magenschleimhaut Arch f
- 4 Holla c Juice as a Function of Its Activity, J 1 in 1943
- 5 Lifson N Varco R L and Vischer M B The Relationship Between the Total Osmotic Pressure of Gastric Juice and Its Acidity Gastroenterology 1 784 1943
- 6 Rehm W S Evidence That the Major Portion of Gastric Potential Originates Between Submucosa and Mucosa Am J Physiol 147 69 1946
- 7 Sawyer P N and Rhoads J F Unpublished data
- 8 Crane F F Davie R E and Longmuir N M Relation Between Hydrochloric Acid Secretion and Electrical Phenomena in Frog Gastric Mucosa Biochem J 43 31 1948
- 9 Rehm W S Effect of Histamine and Hydrochloric Acid on Gastric Secretion and Potential Am J Physiol 141 537 1944
- 10 Crane F F Davie R E and Longmuir N M The Effect of Electrical Current on Hydrochloric Acid Secretion by Isolated Frog Gastric Mucosa Biochem J 43 33 1948

TOTAL GASTRECTOMY

REPORT OF SIXTY THREE CASES

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TWENTY ONE total gastrectomies performed at the Johns Hopkins Hospital by one of us (W P L, II) during the period of July, 1944 to December 1945, were reported in a previous article¹ Since that time forty two additional total gastric resections have been performed by the various members of the surgical staff of the Johns Hopkins Hospital It is the purpose of this article to review the results obtained in this entire group of sixty three cases including the present status of the patients previously reported

MATERIAL

The lesions treated by total gastrectomy in this group of sixty three patients are listed in Table I The indication for total resection of the stomach has been gastric malignancy in all cases but one which was a case of gastroesophageal varicosis This patient was a young man with Banti's syndrome and severe hematemesis who had been subjected to many operative procedures before the introduction of lienorenal anastomosis Subtotal esophagocardectomy was ineffective Total gastric resection has eliminated all signs of hemorrhage from the alimentary tract In all the other cases the operator performed the resection in the belief that he was dealing with a malignant process Three errors in the operator's judgment are indicated by the three patients with benign ulcer who were subjected to total gastrectomy In one of the patients there was a large inflammatory mass around the ulcer the other two had a large ulcer high on the lesser curvature

The rationale of the total gastrectomy for malignant tumor of the stomach is to effect a block removal of the tumor and its primary avenues of invasion as radically as possible together with all regional lymph nodes As Pack² has recently pointed out this is the ideal operation for gastric cancer and is the only technique which embodies the reasoning which is followed in resections of mammary, colonic and rectal carcinoma

OPERATIVE TECHNIQUE

The technical procedure followed in these sixty three cases has been fairly well standardized The details of operative technique were presented in a previous communication¹ An abdominal approach has been used in the majority of instances (Table II), usually an upper midline incision with extension up to the left of the xiphoid has been utilized After determination of the operability of the tumor, removal of the stomach and the great omentum has been carried out in all cases In no instance has this procedure been undertaken when

Read at the meeting of the Society of University Surgeons San Francisco Calif March 24 25 1949

TABLE I TOTAL GASTRECTOMIES (JULY 1 1944 TO DEC 31, 1948)

PATHOLOGIC LESIONS	NUMBER
Carcinoma of stomach	53
Leiomyosarcoma of stomach	1
	1
	1
	1
	1
	3
	63

TABLE II OPERATIVE PROCEDURE IN SIXTY THREE TOTAL GASTRECTOMIES

<i>Operative Approach</i>		
Abdominal	57	
Thoracic	4	
Abdominotheracic	2	
<i>Extent of Resection</i>		
Stomach and omentum		34
Stomach, omentum spleen		37
Stomach, omentum spleen pancreas		5
Stomach, omentum spleen lower esophagus		3
Stomach, omentum colon (transverse)		3
Stomach, omentum colon (transverse) spleen		1
Stomach, omentum left lobe of liver		1
<i>Types of Anastomoses</i>		
Esophagojejunotomy (end-to-side)		57
with enteroenterotomy	4	
additional colonic anastomosis		
Esophagoduodenotomy		6

distant metastases were known to be present. In Table II the organs removed in this series in addition to the stomach and the omentum are shown. These resections were done because of direct extension of the tumor into adjacent viscera excepting the spleen. The spleen was not removed routinely in this series but splenectomy was done when the operator thought there was possibility of extension into the gastrosplenic ligament or when the splenic pedicle was damaged during the course of mobilization of the stomach. In the majority of instances after resection of the stomach an anastomosis was carried out between the end of the esophagus and the side of the jejunum. There were fifty-seven such esophagojejunostomies. The loop of jejunum was usually brought up through a rent in the mesentery behind the transverse colon but in several instances an antecolic type of anastomosis was carried out. An additional enteroenterostomy between the afferent and efferent limbs of the jejunal loop was performed in twenty-four instances. Six patients were treated by esophagoduodenostomy. The feasibility of this procedure which was first demonstrated by Bringham⁴ in 1898 depends on the mobility of the duodenum. The anastomoses between the esophagus and the intestine have been constructed with an outer row of interrupted sutures of medium silk and an inner row of closely placed interrupted sutures of fine catgut or of fine silk. Continuous sutures have been avoided in order to obviate subsequent stricture formation.

POSTOPERATIVE MANAGEMENT

During and immediately after operation 1000 to 1500 cc. of blood have usually been given to these patients. Their postoperative management has been

come fairly well standardized in that they are kept on parenteral feeding with nothing by mouth for a period of four days. On the fourth or fifth day they have been started on a graduated liquid diet beginning with 30 cc of water each hour, increased slowly with the patient's tolerance to a full liquid diet by the sixth or seventh day. The majority of patients have been able to take soft solid diet in six small feedings by the eighth to tenth day. Practically all of them have been discharged on a full soft diet in six small feedings. Supplemental vitamins and ferrous iron have usually been added to this dietary. Penicillin has been administered in full doses in all cases for the first postoperative week, after which it has usually been discontinued. In a few of the more recent cases streptomycin has been added to this prophylactic antibiotic therapy. In most instances prior to discharge a postoperative fluoroscopy with barium has been carried out and also an endoscopic examination. No strictures at the line of anastomosis between esophagus and intestine have been encountered. The majority of patients have been discharged from the hospital by the fourteenth postoperative day.

OPERATIVE MORTALITY RATE AND POSTOPERATIVE COMPLICATIONS

There have been six deaths in the immediate postoperative period among these sixty-three cases of total gastrectomy, an operative mortality rate of 9.5 per cent. The causes of death are given in Table III. Frank leakage at the esophagojejunal suture line has been the cause of death in three instances. In two of these cases it was felt that dehiscence or necrosis at the suture line occurred because of interference with the blood supply of the lower esophagus and in the other case leakage clearly resulted from necrosis of the jejunal wall at the stoma following an effort to construct a food pouch between the limbs of the jejunum.

The postoperative course of the majority of the fifty-seven individuals who survived operation has been quite uneventful. Thirty-seven of these patients had no significant difficulties. In Table IV the postoperative complications

TABLE III POSTOPERATIVE DEATHS IN SIXTY-THREE TOTAL GASTRECTOMIES

PATIENT	OPERATION	SURVIVAL (DAYS)	CAUSE OF DEATH
J. J.	Total gastrectomy, splenectomy, partial colectomy, esophagojejunal anastomosis and ileocolonic anastomosis	1	Leak at anastomosis (esophagojejunal)
F. W.	Total gastrectomy with esophagojejunal anastomosis and long enteroenterostomy	10	Leak at anastomosis (esophagojejunal)
A. H.	Total gastrectomy, splenectomy with esophagojejunal anastomosis	~	Pneumonia
L. W.	Total gastrectomy, splenectomy, partial pancreatectomy with esophagojejunal anastomosis	15	Leak at anastomosis, pulmonary embolism
R. D.	Total gastrectomy, splenectomy with esophagojejunal anastomosis	1	Coronary thrombosis
R. S.	Total gastrectomy with esophagojejunal anastomosis	4	Afferent loop obstruction, uremia, bronchopneumonia
Operative Mortality 9.5%			

TABLE IV POSTOPERATIVE COMPLICATIONS IN SURVIVORS

Thromboembolism	5
Atelectasis	4
Subdiaphragmatic abscess	3
Pneumothorax	2
Pneumonia	2
Pylorospasm	2
Acute pancreatitis	1
Intestinal obstruction	1
Premature labor	1
Fecal fistula	1
Wound abscess	1

of a nonfatal nature are shown. There were no episodes of postoperative bleeding, no eviscerations, and no difficulties encountered with the duodenal stump.

Most of these patients have experienced varying degrees of epigastric fullness after being placed on solid food, but this has not been a particularly distressing symptom. About one third of the survivors have had trouble with epigastric burning during and after meals. This symptom, which is apparently due to reflux of bile and pancreatic juice into the lower esophagus, has been transitory in most instances. It is encountered much less frequently in individuals who have had enteroenterostomy.

A comparison of the mortality rate of total gastrectomy for malignant gastric tumors with the operative mortality for partial gastric resection for such tumors at this clinic in the period covered by this study is given in Table V. This is a selected series in that it covers all the carcinomas and other malignant gastric tumors which have been explored in this hospital since the end of the previous study,¹ added to the twenty-five cases on which that report was based. One hundred forty-four individuals with histologically verified malignant gastric tumor were explored. In fifty-three of these cases the tumor was not resectable. In this group thirteen palliative gastroenterostomies were carried out. Ninety-one patients were treated by resection—a resectability rate of 63 per cent. The combined or over-all resection mortality rate was 13 per cent. The highest mortality rate was encountered in the cases of esophagocardiotomy, and interestingly enough, the operative mortality rate for total gastrectomy (10 per cent) is even less than the mortality rate for partial gastrectomy for gastric malignancy. These data are based on resections carried out for malignant tumors; the total gastrectomies which have been done for benign ulcer, syphilis, and various other

TABLE V SUMMARY OF SURGICAL EXPERIENCE WITH MALIGNANT GASTRIC TUMORS
JULY 1, 1914, TO DEC. 31, 1949

CASES	NUMBER	DEATHS	PER CENT MORTALITY
Explored	144	17	11
Not resectable	53	5	9
Gastroenterostomies	13	2	15
Resected	91	12	13
—	59	6	10
—	23	3	13
—	8	3	37
—	2	0	0
—	Over-all rate	13%	

not included in this group. There have been thirty eight total gastrectomies for gastric cancer since the original report with four deaths an operative mortality rate of 10.5 per cent in the more recent group. Although these data are based on too few cases to have any real statistical significance, nevertheless they indicate that total gastrectomy has become a reasonably safe surgical procedure.

PATHOLOGIC OBSERVATIONS

In twenty five of the fifty five total gastrectomies for carcinoma of the stomach and in the three resections for gastric sarcoma, the stomach was so extensively invaded by tumor that its gross removal would have been impossible by any resection less than total gastrectomy. In the remaining cases the tumor was fairly well localized either in the pyloric antrum or in the cardia so that its gross removal could have been accomplished either by high partial gastrectomy or by esophagocardiotomy. Unfortunately, a careful histopathologic study of the extent of the microscopic invasion of the gastric wall above and below the gross tumor has not been carried out in all cases. Coller Kay and MacIntyre⁴ pointed out that in their experience the surgeon is likely to underestimate the actual margin of neoplasm in the wall of the stomach at operation in about 25 per cent of cases. Atkins⁵ has recently described unpublished work in his department at Guy's Hospital in which careful histologic study of the upper margin of the line of resection in cases of subtotal gastrectomy for carcinoma has demonstrated the presence of malignant cells in eighteen of nineteen cases studied. Coller Kay, and MacIntyre made a careful study of the regional lymphatic metastases of carcinoma of the stomach and found that it was impossible to tell without microscopic section whether the lymph nodes were invaded by metastases unless they were obviously completely replaced by carcinoma. In their cases they found metastases to the regional nodes in 75.5 per cent. In the fifty five patients with carcinoma of the stomach treated by total gastrectomy in this group 72 per cent had lymph node metastases. In Table VI we have divided these fifty five cases of gastric carcinoma into Schindler's⁶ modification of the Borman's⁷ classification of gastric carcinoma, using the relatively loose terms 'limited' and 'infiltrative'. Twenty four of these cases fall into the group of limited carcinoma; thirty one are considered to be 'infiltrative'. Of the twenty four patients with 'limited' carcinoma all but nine had metastases to the regional nodes whereas in twenty five of the thirty one 'infiltrative' carcinomas there were regional node metastases.

These data serve to emphasize the surgeon's lack of ability to judge accurately the extent of invasion of the gastric wall by the tumor and to recall the high incidence of invasion of lymph nodes even in apparently well localized forms of gastric carcinoma.

TABLE VI. RELATION OF LYMPH NODE METASTASES TO GROSS TYPE OF TUMOR (SCHINDLER'S) IN FIFTY FIVE CASES OF GASTRIC CARCINOMA

TYPE OF CARCINOMA	NODES NEGATIVE	NODES POSITIVE	PER CENT POSI- TIVE NODES
Limited	9	15	6
'Infiltrative'	6	25	80
Total	15	40	72

FOLLOW UP STUDIES

In Fig. 1 the present status of the sixty three patients treated by total gastrectomy in this series is summarized. Twenty eight of these (44 per cent) are living today. Eighteen or 29 per cent of the group have lived for one year or more. Eleven of these eighteen are now alive one or more years after operation (18 per cent). Three patients are living more than four years after total resection of the stomach.

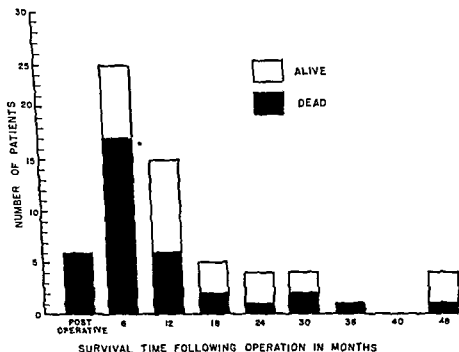


Fig. 1—Present status of 63 patients treated by total gastrectomy. J. H. H. series. July 1, 1944 to Dec. 31, 1948.

Aside from the six postoperative deaths, seventeen patients have died in less than six months after total gastrectomy. It seems obvious in this group by far the majority of whom have died with recurrent carcinoma that total gastrectomy served only as a palliative procedure. All but two of these seventeen patients had extensive tumors with metastases to regional nodes at the time of operation. Biopsy of the tumor was carried out at the time of operation in fifteen cases. The majority of these individuals who died in the first six months after operation would fall into the group representing neglected cases in which the patients first appeared for definitive treatment twelve months or more after the appearance of symptoms of gastric disorder. In most of these cases the tumor was doubtless microscopically far beyond the limits of any possible block excision at the time of operation. It is also possible however that in a few instances the surgeon was guilty of seeding the peritoneum with carcinoma cells by poor technique in taking a biopsy of the tumor prior to resection or by ill

advised manipulation of a tumor which had extended through to the serosal surface of the stomach wall

A majority of these patients after discharge from the hospital have been followed by Paulson* in the gastrointestinal clinic of this hospital. The dietary regimen which he has worked out for them consists primarily of a high caloric high protein, relatively low fat diet in five or six small even feedings daily with supplemental vitamins ferrous iron and some form of protein hydrolysate. Paulson and his associates have made careful studies of the blood, stools, liver function weight, appetite, food capacity, and dietary idiosyncrasies of these patients. Repeated endoscopic examinations have been carried out at intervals and in no instance has any benign stricture of the esophagojejunal or esophagoduodenal junction occurred. In several patients dying of recurrence a malignant obstruction has been demonstrated. In general it seems proper to say that fairly satisfactory biologic adjustment to the loss of the stomach has been made by the majority of individuals exclusive of those who have gone rapidly downhill with recurrent carcinoma. A majority of patients have gained weight after the operation, but as previously observed¹ very few of them have made a gain equal to the weight loss prior to operation. The food capacity of practically all the patients has been somewhat limited and epigastric fullness after meals is a common complaint. Only seven individuals seem to have regained a truly normal food capacity. This fact probably is the explanation for the failure to regain normal weight. Diarrhea has not been a problem. A few patients have had transitory diarrhea in the immediate postoperative period, but none has had lasting difficulties of this type.

Postoperative symptoms of the so called 'dumping' syndrome or perhaps better, the 'intestinal distention' syndrome have been encountered in five individuals. This symptom complex has been transitory in most instances however and has not persisted after the first six months.

Epigastric and substernal distress of a burning type occurring a few minutes after meals has caused considerable difficulty for twenty six patients. This symptom is almost certainly due to the reurgitation of bile and pancreatic juice into the lower esophagus. It has been encountered infrequently in patients with an enteroenterostomy placed below the esophagojejunal anastomosis. In most instances it has responded fairly satisfactorily to the administration of amphogel and has usually proved to be a transitory symptom persisting for only a few months after operation.

made a fair
and 19 of

still eating four to six small meals a day and do not have a problem with
two of the eleven patients have no gastrointestinal symptoms either during or
after meals. The majority complain of some degree of epigastric fullness and
discomfort with or without associated heartburn at the time of or shortly after
meals. All of these patients have normal bowel habits and none of them are

TABLE VII. PATIENTS NOW ALIVE SURVIVING TOTAL GASTRECTOMY FOR ONE YEAR OR MORE

PATIENT	SURVIVAL TIME (MO.)	ALIMENT	FOOD CAPACITY	GI SYMPTOMS	STOOL	WEIGHT	ANEMIA	WOPA	RECURRENT
1 J W	34	Good	Normal	None	Normal	10 lb gain	No	Regular	No
2 J C	32	Fair	4-5 meals per day	Flatulence	Normal	20 lb loss	No	Light	Benign ulcer
3 J I	40	Good	3 meals per day	Heartburn	Normal	13 lb gain	No	Regular	No
4 L S	29	Good	Normal	None	Normal	5 lb gain	—	Regular	Benign ulcer
5 J H	6	Good	Normal	None	Normal	10 lb gain	No	Regular	No
6 H F	22	Fair	6 meals per day	Heartburn	Normal	30 lb gain	No	Regular	No
7 W	21	Good	Normal	None	Normal	20 lb gain	No	Regular	No
8 S C	19	Good	Normal	Heartburn	Normal	20 lb gain	No	None	?
9 B M	16	Good	6 meals per day	Much gas	Normal	35 lb loss	No	Light	?
10 L H	14	Fair	6 meals per day	Flatulence	Normal	20 lb loss	No	Light	?
11 W C	11	Good	Normal	Flatulence	Normal	15 lb gain	No	Regular	No

troubled with diarrhea, although it has been shown previously that because of the incomplete absorption of fats the stool may consist of 20 to 50 per cent of fats

Blood studies have been carried out on all of these patients quite recently with one exception, and in no instance is there anemia. Only one patient shows a slight degree of microcytosis by smear, but her blood indices are within normal limits. A majority of patients are working regularly and have been able to return to their usual occupations. One of these patients is doing heavy labor on a farm. Only two patients are unable to do full time work, and in each instance recurrence of carcinoma is suspected.

DISCUSSION

In selecting an operation for the cure of malignant disease one must consider three factors. First the operative mortality rate or the immediate danger of the operation; second the adequacy of the procedure as a means of eradicating the tumor; third, the compatibility of the end result with continued health of the individual.

Total gastrectomy has now become a relatively safe procedure. In the present series of sixty three cases, the mortality rate was 9.5 per cent. Forty two of these operations were performed by men during the tenure of their surgical residency. As there has been only one death in the last thirty consecutive cases of total gastrectomy in the hospital, the operative mortality for this procedure has been only 3.3 per cent in the last two years of this study. Three of the six deaths in this series of sixty three total gastrectomies are attributable to leakage at the esophagojejunal anastomosis. Esophagojejunostomy is obviously the most dangerous part of the procedure as regards the immediate postoperative course. We have had no experience in this group of patients with the Roux en Y type of anastomosis or with the type of esophagojejunostomy described by Roscoe Graham* in which the anastomosis is buried by suturing the proximal and distal jejunal limbs around it. The end to side type of esophagojejunostomy as done in this series must be carried out with meticulous care in order to be successful. To summarize again the points in this regard: Too extensive mobilization of the esophagus out of the mediastinum is to be avoided because of the danger of impairment of its blood supply and because of the advantage of preserving the layer of fibrous areolar tissue which surrounds the abdominal esophagus. If the jejunal loop is short tension may be avoided by dividing one or more vessels in the base of the mesentery. Interrupted sutures are used throughout in the anastomosis and the internal layer is based on the approximation of the full thickness of the esophageal wall to that of the jejunum with closely placed interrupted inverted sutures with the knots tied on the inside of the lumen. Last the anastomosis is supported by approximating a flap of peritoneum which is elevated from the abdominal esophagus and adjacent diaphragm down to the jejunum below the line of suture. It is our opinion at present that a long enteroenterostomy between the afferent and efferent jejunal limbs is advisable in order to obviate the postoperative 'burning' syndrome.

Pack² recently described total gastrectomy as being the ideal operation for gastric cancer. To quote from his article, 'If an organ is unessential for life the growing concept of cancer therapy more and more suggests sacrifice of the entire organ: the regional lymph nodes, and the intervening lymphatics.' The block resection in total gastrectomy for cancer includes the entire great omentum, the proximal two centimeters of duodenum, the entire stomach, the entire gastrophrenic omentum, the spleen, and the lower two centimeters of the abdominal esophagus. Included in this block are the lymphatics and nodes along the greater curvature of the stomach, the nodes of the lesser curvature, the infrapyloric, retro-pyloric and right gastroepiploic nodes, the nodes of the ligogastric ligament, the juxta-cardiac nodes, and the nodes along the left gastric vessels and around the celiac axis. The peritoneum of the lesser bursa should be removed for any posterior lesion. If there is extension of the tumor into an adjacent organ (for example transverse mesocolon, colon, left lobe of liver, tail of pancreas) such organs should be included in the block resection. Tumors of the cardia of the stomach involving the lower esophagus are best dealt with in our opinion by an abdominothoracic exposure which permits removal of the diaphragm adjacent to the tumor in addition to the entire stomach and the lower esophagus.

The chance for more complete removal of gastric carcinoma and its primary node metastases seems to us to be far greater by total gastrectomy than by partial gastrectomy. The argument that recurrence or death from carcinoma after partial gastrectomy usually is due to metastases rather than recurrence in the gastric stump has been used to question the necessity for total gastrectomy. One wonders if the more adequate removal of the lymphatic drainage areas of the stomach which is made possible by total gastrectomy will negate this argument. We have already pointed out the difficulties of the gross evaluation of the extent of a tumor in the wall of the stomach and have emphasized the high incidence (62 to 80 per cent) of lymph node metastases with gastric carcinoma regardless of whether the individual tumor is limited or infiltrative. These factors certainly militate against the complete eradication of gastric carcinoma by subtotal gastrectomy. Our series of total gastrectomies for gastric carcinoma is too small and covers too short a period of time to permit any statistical comparison with late results obtained by subtotal gastrectomy. It may be pointed out, however, that three patients with gastric carcinoma treated by total gastrectomy in the earlier series survived without evidence of recurrence for four years or more after operation, and none of these patients had a lesion at the time of operation which could have been even grossly removed by partial gastrectomy.

The data presented in Table VII are submitted as evidence that a healthy life is possible after total resection of the stomach. The majority of patients in this series who are now alive after surviving total gastrectomy for one year or more are working regularly, have made a fairly good gain in weight since operation and are leading a normal life with some dietary restrictions and some difficulties of a relatively insignificant nature related to fullness and distress after eating.

In the sixty three total gastrectomies in this series, three errors in diagnosis resulted in three total gastrectomies for benign ulcer. One of these errors, occurring early in the series prompted us to feel that a specimen for biopsy of the carcinoma or of the mass in the stomach should be taken before total gastrectomy is carried out. In the usual case of gastric cancer the diagnosis is obvious, and biopsy may be unnecessary, however, in less advanced cases and particularly when the surgeon is faced with the problem of a large gastric ulcer, biopsy is definitely indicated. It is our opinion that great care should be exercised in biopsy of a gastric cancer because of the danger of seeding the peritoneal cavity with carcinoma cells. Improper technique in biopsy of gastric carcinoma as has been followed in many of the cases of this series may be responsible for some of the deaths from recurrent carcinoma in the first six months after operation. A specimen for biopsy should be taken with the same precautions that are used in biopsy of a carcinoma of the breast. This is best done by placing a gastrotomy incision with the cautery through the stomach wall in a seemingly uninvolved quadrant and taking a segment of the suspected tumor from within the lumen of the stomach. The gastrotomy incision may then be closed by an uncontaminated assistant while the operator changes gloves and gown and discards the instruments used in taking the specimen. This precaution may eliminate or reduce contamination of the peritoneum with malignant cells.

CONCLUSIONS

Sixty three total gastric resections are reported with a mortality rate of 9.5 per cent.

The majority of patients who survive operation without evidence of recurrence for six months or longer adjust themselves to a normal mode of living.

At present, survival times are too short and the number of cases of total gastrectomy too small to compare the late results with those following subtotal resection. There are however theoretical considerations and some actual indications from a series such as is herein presented that total gastrectomy is a more effective treatment of gastric cancer than is subtotal resection.

REFERENCES

- 1 Longmire William P. Jr. Total Gastrectomy for Carcinoma of the Stomach. *Surg., Gynec. & Obst.* 84: 1-1947.
- 2 Jack George T., McNeer G. and Bohrer R. Y. Principles Governing Total Gastrectomy. *Arch. Surg.* 55: 400 1947.
- 3 Brigham Charles B. Case of Removal of the Entire Stomach for Carcinoma. *Success* Boston M. & G. J. 138: 410 1908.
R. S. Regional Lymphatic Metastases of 43 1941.
- 4 ability of Certain Gross Types of Gastric 1946.
- 5 total Gastrectomy. *New England J. Med.* (In
- 6 ectomy. *SLEEP* 8: 2-1940.
- 7 Crisham Ross. Technique of 1941.

OPERATIVE MANAGEMENT OF CARCINOMA OF THE COLON

IS PROXIMAL DRAINAGE OF THE UNOBSTRUCTED COLON NECESSARY?

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THERE is no unanimity of opinion on what is the best operative procedure for carcinoma of the colon without obstruction. The surgeon may elect one of four methods: (1) primary resection and anastomosis without preliminary or concomitant proximal colostomy; (2) resection and anastomosis with proximal colostomy; (3) multiple stage procedures in which anastomosis precedes resection; and (4) the Mikulicz operation.

There is general agreement that if intestinal obstruction is present drainage by cecostomy or colostomy should precede resection.

The majority of surgeons provide drainage of the bowel proximal to the resection when little or no obstruction exists. This is not our policy. It is the practice of both the resident and senior surgeons of this clinic to do resection and primary anastomosis without preliminary or concomitant proximal drainage whenever it is possible. This method is not prescribed as obligatory and the surgeon is free to choose the procedure which in his judgment best meets the indications of the case. Thus our elimination of proximal drainage in the unobstructed patient results from the conviction that it is not necessary. This view is contrary to the impression gained from the literature and from conversations with other surgeons. It appeared desirable to evaluate and compare our results with those of others in order to determine whether or not we were justified in our opinion. A study covering the last two decades is necessary for the recent improvements in preoperative and postoperative care have made a profound change in the outlook. Technical proficiency has remained about the same.

This study evaluates the immediate results from resection of carcinoma of the colon (exclusive of the rectum) at the Strong Memorial Hospital from 1925 through 1947.

HISTORICAL BACKGROUND

Allen¹ in 1937 recommended for carcinoma of the right colon preliminary ileotransverse colostomy and secondary resection. In 1939 Allen and Welch² recommended for all cases of carcinoma of the colon a two stage procedure with prior or complementary proximal decompression of the bowel. In 1943 Allen³ reported an overall mortality of 18 per cent in 186 cases. At that time he recommended preliminary ileotransverse colostomy and aseptic anastomosis for surgery of the right and proximal one third of the transverse colon. He advocated preliminary tube cecostomy in dealing with cancer of the remaining portion of the colon. Allen, Welch and Donaldson⁴ in 1947 reported upon 105

¹Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 1-6, 1949.

In the sixty three total gastrectomies in this series, three errors in diagnosis resulted in three total gastrectomies for benign ulcer. One of these errors occurring early in the series, prompted us to feel that a specimen for biopsy of the carcinoma or of the mass in the stomach should be taken before total gastrectomy is carried out. In the usual case of gastric cancer the diagnosis is obvious and biopsy may be unnecessary, however in less advanced cases and particularly when the surgeon is faced with the problem of a large gastric ulcer, biopsy is definitely indicated. It is our opinion that great care should be exercised in biopsy of a gastric cancer because of the danger of seeding the peritoneal cavity with carcinoma cells. Improper technique in biopsy of gastric carcinoma as has been followed in many of the cases of this series may be responsible for some of the deaths from recurrent carcinoma in the first six months after operation. A specimen for biopsy should be taken with the same precautions that are used in biopsy of a carcinoma of the breast. This is best done by placing a gastrotomy incision with the cautery through the stomach wall in a seemingly uninvolved quadrant and taking a segment of the suspected tumor from within the lumen of the stomach. The gastrotomy incision may then be closed by an uncontaminated assistant while the operator changes gloves and gown and discards the instruments used in taking the specimen. This precaution may eliminate or reduce contamination of the peritoneum with malignant cells.

CONCLUSIONS

Sixty three total gastric resections are reported with a mortality rate of 95 per cent.

The majority of patients who survive operation without evidence of recurrence for six months or longer adjust themselves to a normal mode of living.

At present, survival times are too short and the number of cases of total gastrectomy too small to compare the late results with those following subtotal resection. There are, however theoretical considerations and some actual indications from a series such as is herein presented that total gastrectomy is a more effective treatment of gastric cancer than is subtotal resection.

REFERENCES

- 1 Longmire William P. Jr. Total Gastrectomy for Carcinoma of the Stomach. *Surg., Gynec. & Obst.* 84: 41 1947.
- 2 Pack George T. McNeer C. and Booher R. J. Principles Governing Total Gastrectomy. *Arch. Surg.* 55: 457 1941.
- 3 Brigham Charles B. Case of Removal of the Entire Stomach for Carcinoma. Successful Esophagoduodenostomy. *Recovery*. *Boston M. & H. J.* 138: 415 1894.
- 4 Collier P. A., Kay E. B. and McIntyre R. C. Regional Lymphatic Metastases of the Stomach. *Arch. Surg.* 43: 718 1941.
- 5 Curability of Certain Gross Types of Gastric Cancer. *Arch. Surg.* 43: 718 1941.

Total Gastrectomy. *New England J. Med.* (In press)

9 Graham, Roscoe. Technique for Total Gastrectomy. *SURGERY* 8: 257 1939.

time Wangenstein advocated an aseptic type of anastomosis and felt that preliminary proximal drainage of the bowel was not necessary.

Stone and McLaughlin¹ in 1942 reported 104 cases of resection and immediate anastomosis. They had eleven deaths a mortality rate of 10.6 per cent. They did preliminary cecostomy in only nine cases and did not think it necessary in nonobstructed cases.

Zinnunger and Hoxworth¹⁶ in 1943 reported forty-five cases of one stage resection and anastomosis done from 1937 to 1943. In the absence of obstruction they did not carry out proximal drainage of the bowel. Their mortality rate was 8.8 per cent.

Whipple¹ reported his results in resection and anastomosis from 1933 to 1942. There were 111 resections of the left colon with a mortality rate of 12.6 per cent. 95 ileocolectomies were done with a mortality of 15.8 per cent, 23 resections of the transverse colon carried a mortality rate of 21 per cent.

McNairy and Lands¹⁹ reported thirty-four cases of resection and anastomosis with two deaths. In this series were seven patients with obstruction all treated conservatively. These authors stated: "The shortened hospital stay, the elimination of multiple operations, the savings in time, expense and psychologic trauma together with a low mortality make the procedure of resection with primary open anastomosis one of choice."

McLester¹⁹ stated: "Primary one stage resection and anastomosis may succeed in any part of the colon proper but it should not be performed for tumors in the rectosigmoid and its use elsewhere should be limited to uncomplicated lesions."

PRESENTATION OF CASES

From 1928 through 1947 inclusive 287 patients with carcinoma of the colon (exclusive of rectum) have been operated on. This series does not include patients who have had merely exploratory laparotomy without definitive surgery. It does not include patients who have had colostomy as a palliative procedure. Table I shows the various types of operative procedures which have been carried out. These 287 patients have been operated on by many different surgeons both resident and attending.

In the first decade of the period studied (1928 through 1937) 74 patients were operated upon. In the second decade 213 patients were operated upon.

TABLE I TYPE OF OPERATION DONE IN 287 CASES 1928 TO 1947

OPERATION	1928 TO 1937	1938 TO 1947	TOTAL
Ileocolostomy with resection	0	66	66
Cecocolostomy with resection	23	123	151
Ileocolostomy, 1 stage resection	8	5	13
Colocolostomy, 2 stage resection	1	1	2
Palliative ileocolostomy (no resection)	3	4	7
Palliative colocolostomy (no resection)	4	1	5
Mikulicz type of operation	10	8	23
Total	46	213	259

patients operated upon since 1943. The over all mortality in this group was 2 per cent. Allen⁵ in 1947 stated that he believed in resection and primary anastomosis and had come to believe that the open type of anastomosis was to be preferred to the closed type. He recommended cecostomy only in cases with acute, complete obstruction of the left colon and stated that concomitant cecostomy was rarely employed.

Many surgeons employ the "obstructive resection" described by Rankin. In 1930 Rankin⁶ reported thirty one operations done in this manner with only one death. At that time he pointed out that the operation should never be done in the presence of obstruction—a point which is frequently not appreciated.

In 1941 Rankin⁷ referred to a gross mortality rate of from 6 to 10 per cent as a favorable one and one which any surgical procedure should be expected to relieve. At that time he advised the aseptic type of anastomosis if anastomosis was to be done although still advocating the obstructive type of resection. In regard to preliminary proximal drainage of the bowel Rankin⁷ said: "One may not easily overemphasize the advantage of a complementary decompressive measure in the event one selects a single stage resection in either the right or left colon."

Cattell⁸ in 1943 reported 133 cases of modified Mikulicz resections of the colon. In these cases there were fifteen deaths, a gross mortality of 11.3 per cent. In 1941 thirty three operations were done with one death, representing a 2.7 per cent mortality. Cattell believed this modified Mikulicz procedure to be the operation of choice in carcinoma of the colon.

In 1932 Lahey⁹ recommended that a modified Mikulicz type of procedure be done on the right colon and in 1942 Lahey and Sanderson¹⁰ reported 112 operations done in this manner.

In 1947 Mayo¹¹ stated: "For the past several years we have been performing a one stage right hemicolectomy for the right portion of the colon with an end to end open type of anastomosis between the terminal portion of the ileum and the transverse colon."

Cheever¹² in 1931 reported 154 patients with carcinoma of the colon operated on at the Peter Bent Brigham Hospital from 1913 to 1931. Fifty five of these operations were radical resections; there were fifteen deaths, a mortality rate of 17.6 per cent. He found that when cecostomy was used an 8.5 per cent mortality resulted and that without cecostomy the mortality rate was 24 per cent. He recommended resection and anastomosis in dealing with carcinoma of the colon feeling that the Mikulicz type of procedure should be reserved for those cases with particular indications. He stated: "A general principle so widely accepted that it needs no support is that of the expediency of a preliminary proximal drainage operation."

Wangensteen¹³ discussed aseptic resections of the gastrointestinal tract and reported 100 consecutive cases handled by himself in seven months from March 1940. In this group were fourteen colon resections with one death. Wangenstein¹⁴ reported forty six resections of the colon for carcinoma from 1941 to 1943, there was a mortality rate in this group of 2.1 per cent. At that

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TABLE I TYPE OF OPERATION DONE IN 287 CASES 1928 TO 1947

OPERATION	1928 TO 1937	1938 TO 1947	TOTAL
Ileocolic tumor with resection	20	66	86
Cecocolic tumor with resection	3	128	131
Ileocolostomy distal resection	8	5	13
Colocolic tumor delayed resection	1	1	2
Palliative ileocolostomy (no resection)	3	4	7
Palliative colocolic tumor (no resection)	4	1	5
Mikulicz type of operation	15	8	23
Total	74	213	287

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Many surgeons feel that surgery of the left colon is attended by a higher mortality rate than surgery of the right colon. This has not been true in our series. As shown in Table IV, 106 patients have had ileocolostomy, with 15 hospital deaths, a rate of 14 per cent. 158 patients have had colocolostomy, with 14 hospital deaths, a rate of 8.9 per cent.

TABLE IV. MORTALITY ILEOCOLOSTOMY VERSUS COLOCOLOSTOMY

	ILEOCOLOSTOMY			COLOCOLOSTOMY		
	CASES	DEATHS	PERCENTAGE	CASES	DEATHS	PERCENTAGE
1925-1937	31	0	0	28	7	25
1938-1947	75	6	8	130	7	5.4
Total	106	15	14	158	14	8.9

We have not attempted to break down the deaths into 'medical' or 'surgical' causes or to separate the deaths directly due to surgery and indirectly due to surgery. Any patient who fails to leave the hospital alive, from whatever cause after the operation is classified as a hospital death. Table V shows the proximate cause of death in the 29 cases out of 264. It is to be especially noted that the number of deaths from peritonitis and the number of deaths from surgical shock has been fewer in the second ten year period although more cases have been done in the latter decade.

TABLE V. CAUSES OF DEATH (29 CASES)

	1925 TO 1937	1938 TO 1947	TOTAL
Peritonitis	7	4	11
Surgical shock	4	1	5
Cardiac failure	2	2	4
Pneumonia	2	2	4
Pulmonary embolus	1	-	1
Cerebral hemorrhage	0	1	1
Infection and sepsis	0	1	1
			29

Preliminary or concomitant proximal decompression of the bowel has been carried out only in those patients with demonstrable large bowel obstruction. It has not been used in cases with no obstruction. Table VI shows the comparative mortality for those cases in which proximal decompression was done and for those in which it was not done. In the second decade 42 operations involving bowel anastomosis have been done with proximal drainage. In this group there have been 2 deaths, a mortality rate of 4.7 per cent. During the same period of time 163 operations involving bowel anastomosis have been done without proximal drainage. In this group there have been 11 deaths, a mortality rate of 6.7 per cent.

TABLE VI. RELATION OF PROXIMAL DRAINAGE OF THE BOWEL TO MORTALITY

	PROXIMAL DRAINAGE			NO PROXIMAL DRAINAGE		
	CASES	DEATHS	RATE (PER CENT)	CASES	DEATHS	RATE (PER CENT)
1925 to 1937	19	0	0	40	14	35
1938 to 1947	42	2	4.7	163	11	6.7

In each case material for pathological examination was obtained and the diagnosis of carcinoma confirmed by microscopic examination. There were 100 patients with carcinoma of the left colon, 39 with carcinoma of the transverse colon and 98 with carcinoma of the right colon.

In Table I it can be seen that in only 23 instances was a Mikulicz procedure or one of its modifications carried out. Of the remaining 264 cases 106 patients had an operation which involved an ileocolostomy and 158 had a procedure which involved colocolostomy.

MORTALITY

Of the twenty three patients who had one of the Mikulicz procedures there were six hospital deaths a gross mortality of 26 per cent. The Mikulicz procedure has been reserved for cases with special indications—frequently poor risk patients and those with obstruction. It has not been popular because of the high morbidity rate, the prolonged hospitalization and the feeling that a radical resection cannot be carried out in this manner. If more favorable cases were treated by this method the resultant mortality would probably be appreciably lower.

In operations involving a bowel anastomosis the gross over all mortality for the twenty year period has been 11 per cent. The mortality for the years 1928 to 1937 during which time 59 cases were done was 27 per cent. The mortality for the years 1938 to 1947 when 205 cases were done was 6.3 per cent. These figures are shown in Table II.

TABLE II GROSS MORTALITY IN 287 CASES

OPERATION	CASES	DEATHS	PERCENTAGE
Mikulicz type of operation	23	6	26
Operation involving anastomosis			
1928-1937	59	16	27
1938-1947	205	13	6.3
Total	287	35	11

One sometimes hears the comment that resident surgeons should not do large bowel surgery because of the resultant high mortality. We agree completely that inexperienced surgeons in training should have close supervision when doing this type of work. The policy of this hospital is to supervise the resident surgeon until he attains sufficient proficiency to justify his assuming complete operative responsibility. This policy does not result in an increased mortality rate as shown in Table III. During the second ten year period resident surgeons have operated on 76 patients with carcinoma of the colon and done anastomosis in each; there have been 5 hospital deaths a percentage of 6.6 per cent. During the same ten year period the attending surgeons have operated in 129 cases; there have been 8 hospital deaths a mortality rate of 6.2 per cent.

TABLE III COMPARISON OF MORTALITY FOR ATTENDING SURGEONS AND RESIDENT SURGEONS IN ANASTOMOSIS OF COLON

	CASES	RESIDENT DEATHS	PERCENTAGE	CASES	ATTENDING DEATHS	PERCENTAGE
1928-1937	6	1	16	53	10	28
1938-1947	76	5	6.6	129	8	6.2

As far as the technique of the surgery is concerned we agree with those who say "Less depends on the method used than on the manner of execution" Whipple¹¹ listed three principles to successful bowel anastomosis (1) maintenance of adequate blood supply (2) accurate apposition of serosa and (3) avoidance of tension These principles must be observed for successful surgery It is felt that late leaks from an improperly executed suture line are most often responsible for peritonitis and intra abdominal abscesses In this series "open" and "closed" anastomoses, with and without special clamps have been done There results no demonstrable difference in mortality or morbidity

Our present postoperative routine includes a duodenal indwelling tube which is left in place and connected to suction until the patient passes gas per rectum Clear liquids only are allowed by mouth until intestinal motility is restored Enemas are avoided Whole blood electrolytes fluid and protein are replaced as needed Ambulation on the first or second postoperative day is encouraged unless there is specific contraindication to such activity Rebreathing exercises with a paper bag or hyperventilation with an oxygen carbon dioxide mixture is used Leg exercises by the patient when in bed are mandatory

SUMMARY AND CONCLUSIONS

- 1 The records of all patients who have had definitive surgery for carcinoma of the colon exclusive of rectum at the Strong Memorial Hospital from 1928 to 1947 have been studied
- 2 There were 264 patients who had a type of operation which involved a bowel anastomosis
- 3 The gross uncorrected mortality rate for the second of two ten year periods has been 63 per cent
- 4 Resection and anastomosis is our method of choice in dealing with carcinoma of the colon
- 5 Preliminary or concomitant proximal drainage of the bowel has rarely been used in the cases with no obstruction It is felt that the results here reported justify this policy

REFERENCES

- 1 Allen A W Right Colectomy for Malignant Disease J A M A 109 923 928 1937
- 2 Allen A W and Welch C F Malignant Disease of Colon Am J Surg 46 141 160 1939
- 3 Allen A W Carcinoma of the Colon SURGERY 14 340 350 1943
- 4 Allen A W Welch C F and Donaldson C A Carcinoma of Colon Ann Surg 126 1930 1941
- 5 Allen A W Carcinoma of Large Intestine S Clin North America 27 1018 1031 1947
- 6 Rankin F W Resection and Obstruction of Colon (Obstructive Pesection) Surg Gynec & Obst 50 494 504 1950
- 7 Rankin F W Principles of Surgery of Colon Surg Gynec & Obst 72 332 340 1941
- 8 Cattell Richard B Carcinoma of Colon and Rectum SURGERY 14 378 386 1943
- 9 Inghes F H Resection of Right Colon and Anastomosis of Ileum to Transverse Colon After Mikulicz Plan Surg Gynec & Obst 54 923 929 1932
- 10 Lahay F H and Sander on L Lesions of Right Colon Involving Right Colectomy J A M A 120 1330 1341 1942
- 11 Mayo C W Carcinoma of the Right (Proximal) Portion of the Colon S Clin North America 27 875 883 1947
- 12 Cheever D Choice of Operation in Carcinoma of Colon Ann Surg 94 705 716, 1931

MORBIDITY

We have compared the morbidity rate for ileocolostomy and for colocolostomy. All postoperative complications however minor, are tabulated. Again no attempt has been made to separate complications directly and indirectly due to operative technique. Furthermore any patient remaining in the hospital longer than 21 days even though a specific complication has not been observed is classified as a complicated case. The average duration of the postoperative stay in uncomplicated cases has been 15.4 days.

The morbidity rate for ileocolostomy and for colocolostomy for the two ten year periods has been compared. This is shown in Table VII. Of 106 cases involving ileocolostomy there have been 33 complicated cases a rate of 31 per cent. Of 158 cases involving colocolostomy, 53 cases have been complicated a rate of 34 per cent.

TABLE VII. MORBIDITY, ILEOCOLOSTOMY VERSUS COLOCOLOSTOMY

	1934 TO 1943			1933 TO 1941			TOTAL		
	CASES	COMPLICATIONS	PER CENT	CASES	COMPLICATIONS	PER CENT	CASES	COMPLICATIONS	PER CENT
Ileocolostomy	31	1	3.2	75	21	28	106	22	21
Colocolostomy	28	12	43	130	41	31	158	53	34

Table VIII shows the type and frequency of the complications encountered. It can be seen that wound infections have been most frequent in the second ten year period and deaths from peritonitis less frequent.

TABLE VIII. ANALYSIS OF COMPLICATIONS IN OPERATIONS WITH ANASTOMOSIS

COMPLICATION	1934 TO 1943	1933 TO 1941	TOTAL
Wound infection	2	17	19
Prolonged hospitalization (no specific complication noted)	3	7	10
Prolonged hospitalization for closure of colostomy	2	11	13
Wound disruption	0	0	0
Abdominal abscess	7	0	7
Urinary tract complications	0	7	7
Intestinal obstruction	3	2	5
Fecal fistula	4	0	4
Pulmonary emboli	0	4	4
Pneumonia atelectasis	0	0	0
Fever undetermined origin	2	0	2
Thrombophlebitis	0	1	1
Total number of complicated cases			83
Total number of cases			264
Gross morbidity rate			31%

MANAGEMENT

Lankin¹ listed some 'safety factors' to be observed in surgery of the colon. Those dealing with preoperative care are (1) relieving obstruction (2) combating dehydration, discoloration and anemia during the preoperative period (3) local cleansing of the bowel and eliminations of infections both by lavage and by chemotherapy (4) evaluation of the physiologic reserve of the patient based on laboratory evidence as well as physical examination and appearance. These are sound principles and must be observed if one is to carry out successful colon surgery.

As far as the technique of the surgery is concerned, we agree with those who say "Less depends on the method used than on the manner of execution" Whipple¹⁷ listed three principles to successful bowel anastomosis (1) maintenance of adequate blood supply (2) accurate apposition of serosa, and (3) avoidance of tension. These principles must be observed for successful surgery. It is felt that late leaks from an improperly executed suture line are most often responsible for peritonitis and intra abdominal abscesses. In this series 'open' and 'closed' anastomoses with and without special clamps have been done. There results no demonstrable difference in mortality or morbidity.

Our present postoperative routine includes a duodenal indwelling tube which is left in place and connected to suction until the patient passes gas per rectum. Clear liquids only are allowed by mouth until intestinal motility is restored. Enemas are avoided. Whole blood electrolytes fluid and protein are replaced as needed. Ambulation on the first or second postoperative day is encouraged unless there is specific contraindication to such activity. Rebreathing exercises with a paper bag or hyperventilation with an oxygen carbon dioxide mixture is used. Leg exercises by the patient when in bed are mandatory.

SUMMARY AND CONCLUSIONS

1 The records of all patients who have had definitive surgery for carcinoma of the colon exclusive of rectum at the Strong Memorial Hospital from 1928 to 1947 have been studied.

2 There were 264 patients who had a type of operation which involved a bowel anastomosis.

3 The gross uncorrected mortality rate for the second of two ten year periods has been 6.3 per cent.

4 Resection and anastomosis is our method of choice in dealing with carcinoma of the colon.

5 Preliminary or concomitant proximal drainage of the bowel has rarely been used in the cases with no obstruction. It is felt that the results here reported justify this policy.

REFERENCES

- 1 Allen A W Right Colectomy for Malignant Disease J A M A 109 9:3 928 1937
- 2 Allen A W and Welch C E Malignant Disease of Colon Am J Surg 46 171 180 1953
- 3 Allen A W Carcinoma of the Colon SURGERY 14 3:3 36 1943
- 4 Allen A W Welch C E and Donaldson G A Carcinoma of Colon Ann Surg 126 19 30 1947
- 5 Allen A W Carcinoma of Large Intestine S Clin North America 27 1019 1031 1947
- 6 Pankin F W Resection and Obstruction of Colon (Obstructive Resection) Surg Gynec & Obst 50 504 509 1930
- 7 Rankin F W Principles of Surgery of Colon Surg Gynec & Obst 72 332 340, 1941
- 8 Cattell Richard B Carcinoma of Colon and Rectum SURGERY 14 3:3 386 1943
- 9 Lahey F H Resection of Right Colon and Anastomosis of Ileum to Transverse Colon After Mikulicz Plan Surg Gynec & Obst 54 923 929 1932
- 10 Lahey F H and Sanderson E Lesions of Right Colon Involving Right Colectomy, J A M A 120 175 176 1942
- 11 Mayo C W Carcinoma of the Right (Proximal) Portion of the Colon S Clin North America 27 8 553 1947
- 12 Cheever D Choice of Operation in Carcinoma of Colon Ann Surg 94 707 716, 1931

MORBIDITY

We have compared the morbidity rate for ileocolostomy and for colocolostomy. All postoperative complications however minor are tabulated. Again no attempt has been made to separate complications *directly and indirectly due to operative technique*. Furthermore any patient remaining in the hospital longer than 21 days, even though a specific complication has not been observed, is classified as a complicated case. The average duration of the postoperative stay in uncomplicated cases has been 15.4 days.

The morbidity rate for ileocolostomy and for colocolostomy for the two ten year periods has been compared. This is shown in Table VII. Of 106 cases involving ileocolostomy, there have been 33 complicated cases a rate of 31 per cent. Of 158 cases involving colocolostomy 53 cases have been complicated a rate of 34 per cent.

TABLE VII MORBIDITY ILEOCOLOSTOMY VERSUS COLOCOLOSTOMY

	1918 TO 1927			1928 TO 1937			TOTAL		
	CASES	COMPLICATIONS	PER CENT	CASES	COMPLICATIONS	PER CENT	CASES	COMPLICATIONS	PER CENT
Ileocolostomy	31	12	33	75	21	28	106	33	31
Colocolostomy	28	12	43	130	41	31	158	53	34

Table VIII shows the type and frequency of the complications encountered. It can be seen that wound infections have been more frequent in the second ten year period and deaths from peritonitis less frequent.

TABLE VIII ANALYSIS OF COMPLICATIONS IN OPERATIONS WITH ANASTOMOSIS

COMPLICATION	1918 TO 1927	1928 TO 1937	TOTAL
Wound infection	~	17	19
Prolonged hospitalization (no specific complication noted)	3	7	10
Prolonged hospitalization for closure of cecostomy	2	11	13
Wound disruption	0	0	0
Abdominal abscess	7	0	7
Urinary tract complications	0	7	7
Intestinal obstruction	1	~	1
Fecal fistula	4	0	4
Pulmonary embolus	0	4	4
Pneumonia atelectasis	0	2	2
Fever undetermined origin	~	0	~
Thrombophlebitis	0	1	1
Total number of complicated cases			80
Total number of cases			204
Gross morbidity rate			39%

MANAGEMENT

Rankin¹ listed some safety factors to be observed in surgery of the colon. Those dealing with preoperative care are (1) relieving obstruction (2) combating dehydration, desiccation and anemia during the preoperative period (3) local cleansing of the bowel and eliminations of infections both by lavage and by chemotherapy (4) evaluating the physiologic reserve of the patient based on laboratory evidence as well as physical examination and appearance. These are sound principles and must be observed if one is to carry out successful colon surgery.

EXCISION OF THE MANDIBLE FOR NEOPLASTIC DISEASE

INDICATIONS AND TECHNIQUES

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RESECTION of the lower jaw is not a common procedure, although it is an operation that has been a standard part of the surgical repertoire for many years. The infrequency of this operation is due to several factors, the principal ones being lack of understanding of the necessity for it in certain situations and a natural reluctance to perform what is generally considered to be a mutilating and incapacitating removal of tissue. Furthermore, the mortality rate has been high and the cure rates low—the two approaching each other to the point of negation.

The angle of the mandible has been the 'no man's land' of the surgical specialties: the general surgeon, the therapeutic radiologist, the plastic surgeon, the otolaryngologist, the oral surgeon, and the dental surgeon all meeting warily at this anatomic point with the result that none has staked out a valid claim. Re-evaluation of the indications and techniques for excision of the mandible are in order, however, because of changing concepts of the reasons for such a procedure and because recent advances in the ancillary surgical sciences have greatly increased the safety of such operations. Improvements in anesthesia and the development of antibiotics have together decreased the mortality and morbidity of this type of surgery to such an extent and as a corollary have so extended the anatomic limits of excision that a point of increasing returns has been reached.

It has therefore seemed worth while to review our cases in which partial segmental or hemiresection of the mandible was performed. Seventy-three patients are included in this study, sixty-nine of whom had excisional surgery other than biopsy. Four patients with tumors metastatic to the jaw or with jaw involvement secondary to a systemic neoplastic disease are included in the group because they are a necessary consideration in differential diagnosis of surgical diseases of the jaw. Many more patients referred for consideration of surgery are excluded because they were in a preterminal and untreatable condition with such hopelessly far advanced cancer that only palliative gestures could be made.

Tables I, II, III, and IV show the distribution of tumors in which excisional surgery of the jaw was considered. One is immediately impressed by the fact that tumors arising from the mandible itself constitute only a small part of the total group of tumor cases in which jaw surgery is necessary. This illustrates a recent and fundamental change in jaw surgery, namely, much greater emphasis on resections of the mandible in the surgical attack on intraoral cancer. Only 15 of our patients were operated upon for tumors arising primarily from the mandible itself, whereas 49 patients had

Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 1-4, 1949.

- 13 Wangenstein, O H Aseptic Reactions in Gastrointestinal Tract With Special Reference to Reaction of Stomach and Colon, Surg Gynec & Obst 72 257-51 1941
- 14 Wangenstein O H Primary Reaction (Closed Anastomosis) of Colon and Rectosigmoid Including Description of Abdominoanal Methods for Restoration of Continuity Accompanying Excision of Carcinoma of Rectal Ampulla, SURGERY 14 403-432, 1943
- 14 366-377 1943
Colon, SURGERY 14
- 18 McNesly R W and Lands V G Primary Anastomosis in Treatment of Carcinoma of Colon SURGERY 21 283-296 1947
- 19 MacFee W F Management of Carcinoma in the Several Parts of Colon, Ann Surg 126 125-139 1947

the right mandible with a clinical diagnosis of inoperable osteogenic sarcoma. Roentgenologic studies revealed a large irregular osteolytic defect with a pathologic fracture through the mandible. The clinical diagnosis seemed obvious, yet surgical exploration revealed the lesion to be an eosinophilic granuloma which has remained completely healed for five years following simple curettage. Three other patients had been allowed to develop huge tumors over periods of twelve to twenty years under the mistaken clinical impression that they were malignant and hopeless. All three tumors were benign ossifying fibromas and have been completely eradicated by resection of the jaw. Surgical measures of this extent would have been totally unnecessary if the lesions had been explored and defined microscopically early in their course.

The adamantinomas have been too long regarded as relatively benign lesions of very slow growth and incapable of metastasis. These considerations are not entirely correct since adamantinomas can produce tremendous destruction and very rarely one will metastasize and kill by secondary extension. Most of them are very slow growing tumors but they usually begin relatively early in life and after fifteen or twenty years of repeatedly inadequate therapeutic procedures they usually have produced considerable deformity and suffering. It is our belief that this should be obviated by early recognition of the seriousness of the disease and treatment by segmental resection of the jaw and repair by delayed or immediate bone graft. Since adamantinomas arise in the alveolar ridge side of the mandible it would seem unnecessary to eradicate the entire depth of the bone in all cases and in early cases it should be possible to resect the involved area completely. This can not be done by curettage which is the usual ineffectual treatment. A planned excision of the area would seem to be the procedure of choice but it has not been our privilege to encounter in early and previously untreated case of this tumor.

In the usual advanced and multiple recurrent adamantinoma the tumor has been allowed to progress to a point where segmental or total resection of the jaw is required (Figs 1 and 2). Careful roentgenologic estimate of the extent of bone involvement can sharply delimit the extent of excision of bone. Where full thickness of the mandible has been destroyed and soft tissues have been invaded the tumor usually creates a pseudocapsule about itself by compression plus reactive fibrosis so that its limits can be determined fairly accurately by palpation. These factors allow complete excision of the ordinary adamantinomas whether they be early or far advanced. The fundamental premise in the treatment of adamantinomas is the cognizance that they will all create serious destruction and deformity if allowed to pursue their natural history.

The ossifying fibroma in our series is a tumor of as frequent occurrence as the adamantinoma. The salient features of these two tumors deserve equal emphasis because they are antithetical. Whereas the adamantinoma is a malignant lesion too often considered relatively benign the ossifying fibroma on the other hand is a benign lesion whose growth po-

resection of the jaw for tumors arising in tissues adjacent to this bone. Of this last group in 35 patients the jaw was involved by the tumor by secondary invasion and in 14 the jaw was not implicated but was resected as a necessity in the surgical approach to intra oral cancer.

TABLE I TUMORS OF THE JAW

Tumors of contiguous tissues adjacent to or in involving mandible	49
Primary in mandible	15
Radiation damage to mandible	5
Metastatic to mandible	4
Total	73

TABLE II PRIMARY TUMORS OF INFERIOR MAXILLA

Adamantinoma	4
Ossifying fibroma	4
Giant cell epulis	3
Osteogenic sarcoma	2
Central giant cell tumor	1
Eosinophilic granuloma	1
	15

TABLE III TUMORS METASTATIC TO MANDIBLE

Multiple myeloma	2
Breast carcinoma	2
	4
INCIDENTAL DAMAGE TO MANDIBLE BY TREATMENT TO ADJACENT TUMORS	
Radionecrosis	5

TABLE IV TUMORS OF CONTIGUOUS TISSUE ADJACENT TO OR INVOLVING MAXILLAE

Primary Carcinoma of	
Gingiva	15
Tongue	12
Floor of mouth	10
Lip	6
Buccal mucosa	3
Submaxillary salivary gland	2
Skin	1
	43
35 involved jaw	
14 jaw free	
RECURRENT DISEASE INVOLVING MANDIBLE WITH LIMITED SURGERY	
14 patients all dead within 18 months of recurrent disease	

Primary Tumors of the Jaw—The tumors arising from the jaw itself in this series are listed in Table II. Radicular cysts are not included. Although all possible jaw tumors did not occur in this series it is representative enough to illustrate and to emphasize several important points. Most jaw tumors are not particularly dangerous and are quite amenable to treatment. We should not accept a clinical and roentgen diagnosis of grave prognosis without biopsy proof and attempt at eradication. Four of our cases illustrate this well. One was a 4-year old boy referred with a large painful swelling at the angle of

section. The bone will regenerate surprisingly well although in some relatively advanced cases precautions must be taken against pathologic fracture while healing occurs.

In the very advanced case where the thinning of bone has progressed to complete destruction and replacement of the mandible by tumor, segmental resection is the only recourse (Figs 3, 4 5 and 6). It is this type of problem that should be prevented by early recognition and adequate surgical management long before such destruction takes place.

The giant cell epulis is a not infrequent benign tumor arising from the periosteum of the jaws. Clinical diagnosis is easy and the histologic picture is quite characteristic. Treatment is effective and consists of excision and curettage of the involved area of bone and periosteum, usually a relatively superficial and minor procedure.

The central giant cell tumor is a much more rare lesion, although its microscopic pattern is essentially similar. These tumors arise centrally in the jaw and will expand and destroy the bone causing pathologic fracture. Our only instance of this tumor occurred in the horizontal ramus of a 19 year old girl whose jaw was almost completely eroded by the growth. An intrioral approach and resection of the covering shell of bone followed by wide curettage and irradiation have resulted in a five year cure with complete functional regeneration of the mandible on that side. Whether or not the irradiation was necessary is not known but the analogy to epiphyseal giant cell tumors of long bones seemed reasonable.

Before any treatment of central giant cell tumors of the jaw is undertaken appropriate studies should be made to detect hyperparathyroidism. In the upper jaw particularly giant cell tumors may be caused by such disturbed calcium metabolism and local treatment in such an instance is both ineffectual and unnecessary.

Osteogenic sarcoma of the jaw is fortunately a rare tumor. Our experience is limited to two patients both of whom were total failures of treatment. Both patients had been treated previously and had recurrent disease when first seen. These tumors usually kill by local extension rather than metastatic involvement and it would seem that the problem in these cases is twofold: first a more accurate pathologic appraisal of the lesion, second a much more critical evaluation by the surgeon of the pathologist's report when the diagnosis is that of primary malignant bone tumor. These tumors which kill by regional rather than distant involvement are theoretically curable but the surgeon must be well aware of the lethal potential of such a lesion when he assumes responsibility for its excision.

Tumors Involving the Mandible Secondarily—The principal change in jaw surgery for neoplastic disease has been the marked increase in the surgical attack on intrioral cancer. Invasion of the mandible by carcinomas of the adjacent mucous membranes is far more common than the incidence of malignant tumors primary in the jaw itself. The resurgence of the surgical treatment of these situations has been due to two factors: first recognition that it is practically impossible to sterilize squamous cell carcinoma in bone by ir-

tential is too often considered to be malignant. Both errors have about equally disastrous results. The young fibroma is a discrete, circumscribed, and encapsulated tumor which can be excised completely without loss of jaw tissue. If not enucleated early in their course they will continue to grow slowly until extensive deformity can result from pressure destruction of bone and soft tissues. The usual error in their recognition is pathologic interpretation of a biopsy as osteogenic sarcoma. Such a diagnosis usually eventuates in a fatalistic attitude of hopelessness so that nothing is done and the patient ends up ten to fifteen years later as a derelict freak. Apparently the growth of these benign ossifying fibromas of bone is not biologically self limited, as for instance, are uterine "fibroids." The slow inexorable growth of these jaw tumors can create repulsive asymmetry, which could be completely and simply obviated early in their course by accurate definition of the lesion and adequate surgical management.



Fig 1



Fig 2

Fig
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Treatment of 'ossifying fibromas' is entirely surgical, radiation being useless. In the early cases where the jaw has not been replaced by the tumor they will appear as radiolucent rounded and usually unilocular osteolytic defects with spotty areas of calcification. Surgical approach to the mandibular tumors should be external by turning up a curved neck flap with preservation of the lower (oral) branch of the facial nerve. The periosteum over the involved area of mandible should be stripped and preserved and the external table of the bone resected. The tumor can then be enucleated by careful dis-

radiation methods and that in the occasional case where this may be accomplished the jaw will be so destroyed by the treatment that it will have to be removed anyway because of radionecrosis and osteomyelitis, second, advances in surgical techniques and anesthesia have allowed a much more radical operative attack with a reasonable mortality rate.

The advances in surgical technique are in two categories. Preoperative preparation of the patient is essentially the same nutritional problem as in pyloric obstruction or other major gastrointestinal surgery. Patients with advanced mouth cancer are frequently in as bad or worse condition than candidates for esophageal or abdominal surgery, and the same steps must be taken to correct protein deficiency, electrolytic imbalance, panhypoproteinemia and anemia. The use of antibiotics has contributed tremendously to the safety of these operations, their use in the postoperative period being essential. The other phase of advance in surgical technique involves better anatomic concepts of the spread of intraoral cancer and of the possibilities for surgical elimination of the disease. The advances in plastic surgery have also greatly improved our techniques of repair. These phases will be discussed in further detail.

Advances in anesthesia technique consist essentially in improved methods of isolation and control of the airway, the use of the newer drugs such as sodium pentothal being of minor contributory importance. Intratracheal anesthesia is mandatory so that the airway can be completely sealed from the operative field, blood and mucous secretions thus being blocked from access to the lung. The intratracheal tube may be inserted transnasally through the larynx and an inflatable cuff used to seal the trachea, or the pharynx may be packed with gauze after insertion of the tube. Both precautions are usually done. A preliminary tracheostomy may be necessary in some cases where trismus or tumor growth prevent intubation. This latter technique is used routinely in some clinics and the anesthetic is then administered through the tracheostomy tube. Since a temporary tracheostomy is always required for the immediate postoperative period anyway, this last seems reasonable. There are some cases however in which operability of advanced disease cannot be determined except by examination under general anesthesia and the authors have been able to avoid several futile major operations let alone tracheostomies by the routine of general anesthesia intubation examination in the operating room in doubtful cases and execution of tracheostomy as the final step if the operative procedure is carried out.

The present surgical approach to intraoral cancer invading the mandible consists of a radical neck dissection on the involved side with removal of the hemimandible and all adjacent involved soft parts in continuity. Repair is immediate and a temporary tracheostomy is performed at the same time. The neck dissection is the usual formal en bloc dissection with removal of the sternomastoid muscle and the internal jugular vein but the excision of the jaw and intraoral soft parts allows considerable variation of technique according to anatomic extent of tumor invasion.



Fig 3



Fig 4



Fig 5



Fig 6

Fig 5. Patient with an ill-fitting fibrous mesh in place to resect the tumor. Fig 6. Patient with the mesh replaced by tumor three and two years later.

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The present surgical approach to intracranial cancer involving the mandible consists of a radical neck dissection on the involved side with removal of the hemimandible and all adjacent involved soft parts in continuity. Repair is immediate and a temporary tracheostomy is performed at the same time. The neck dissection is the usual formal en bloc dissection with removal of the sternomastoid muscle and the internal jugular vein but the excision of the jaw and intraoral soft parts allows considerable variation of technique according to anatomic extent of tumor invasion.

Historically the evolution of such a radical surgical technique and the reasons for it are of some interest. Bloodgood was one of the first to devise a limited operation through an external approach for excision of the jaw when involved by tumor of adjacent soft parts. The procedure was almost completely discarded because of the high mortality and low cure rates. As radiation techniques improved so rapidly and seemed so promising that the use of radiation became the accepted and almost universal treatment of intraoral cancer—a situation which still holds today. With the extended use of radiation techniques for intraoral excision of the mandible were developed of necessity for the resultant frequent radionecrosis. These were then applied to cancer involving or adjacent to the mandible, recurrent or persistent after irradiation. In the meantime the rationale and techniques for neck dissection were developed and became the treatment of choice for cervical node metastasis from intraoral squamous cell carcinoma. Thus, the treatment of intraoral cancer was divided into two parts: irradiation of the primary being the usual procedure and surgical treatment of the secondary cervical metastases being a separate consideration. In the meantime the development of the concept of the ideal cancer operation was perfected by many workers: Simpson, Handley, Halsted, and Meyer to name a few contributing the technique of the radical mastectomy. Miles in England devised the abdominoperineal resection of cancer of the rectum and Cade has stated in general the principle of excision of the primary lesion, the intervening lymphatics and the regional lymph nodes as being the ideal cancer operation exemplified by the operations just named. Park² has aptly called this principle "excision and dissection in continuity," applied in his studies to surgical treatment of malignant melanoma. It remained for Martin¹ and his associates on the Head and Neck Service of the Memorial Hospital New York N. Y. to apply this concept to intraoral cancer and they worked out the technique for the procedure outlined here. Grant Ward³ in a presentation before the James F. Wing Society in New York in January 1949 discussed his series of combined neck and jaw procedures and stated that he had done his first one twelve years previously.

Theoretically this concept of en bloc removal of the primary lesion, the intervening tissues and the regional nodes is more applicable to intraoral cancer than to many other tumors for one important reason: squamous cell or epidermoid carcinoma of the oral mucous membranes has a very minimal tendency to invade veins and thus produce distant metastases. These tumors usually remain confined to the head and neck area and kill by local extension and interference with the airway, blood vessels and food passages. This is in contradistinction to breast cancer with its marked propensity for venous invasion or gastrointestinal cancer with the portal system and liver and the peritoneal cavity as avenues of spread in addition to the lymphatics.

Prior to four years ago we did not have a single five year cure in patients with intraoral cancer invading the mandible; in fact the longest survival after treatment was eighteen months. Radiation patients were all dead within one year. At that time seventeen patients had been treated by him

ted surgery, either intraoral resection of the involved mandible, or staged combinations of partial or radical neck dissections plus excision of the mandible. This was sometimes done for local recurrence in the jaw, after neck dissection, a timing not of our choice. Table IV illustrates the results in this group of patients. Not a single patient was salvaged. At that time we applied the more extensive procedure of full radical neck dissection hemimandibulectomy and resection of soft part involvement plus tracheostomy as a one stage procedure. At first only those patients with obvious excavation of the mandible and positive cervical node metastases were subjected to this procedure. Our first two patients so treated are now alive and well at the end of 3½ years. These patients recovered so well that the indications have been extended and to date thirty two such operations have been performed. The salvage rate to date is shown in Table V. It is realized that this is too small a number to be of statistical significance and no case is of five years duration yet the contrast to our preceding experience is so great that it is felt to be worth recording. In this type of cancer, a three year survival is probably a valid cure rate, as

TABLE V COMBINED OPERATION FOR PRIMARY OF PRECURRENT DISEASE

ALIVE FREE OF DISEASE	
Free of disease	
2	42 months
1	7 months
1	24 months
1	2 months
1	17 months
2	12 months
1	10 months
2	9 months
1	5 months
1	4 months
2	1 months
-	1 month
1	
ALIVE WITH RECURRENCE	
Alive	
1	17 months
1	9 months
1	4 months
1	2 months
4	
DIED WITH DISEASE	
Died	
1	24 months
1	18 months
1	12 months
1	11 months
1 (the)	10 months
2	9 months
1	7 months
1	5 months
4	
DIED POSTOPERATIVELY	
Died	
1	3 days (age 86)
1	6 days
(Both died of cardiac failure)	

all our recurrences with one exception were apparent within ten months and averaged five months. The one exception had recurrence in the twelfth month.

Indications for the Operation of Combined Neck and Jaw Resections—At the present time we consider the indications for this type of procedure to be in two categories: the absolute and the relative. The absolute indications would consist of clinical situations where squamous cell carcinoma of the buccal mucosa, gingiva or floor of the mouth has invaded the mandible by direct extension and has produced cervical node metastases. There is no way to salvage such a patient other than by radical neck dissection, excision of the hemimandible and radical excision of the involved soft parts all in continuity. Adenocarcinoma or mucopidermoid carcinoma of the major or intraoral minor salivary glands can produce the same anatomic problem. Another absolute indication is postirradiation recurrence or persistence of cancer involving soft tissues adjacent to the mandible, whether or not the jaw is involved and whether or not cervical node metastases is evident. For extensive tongue lesions recurrent after irradiation with or without clinically apparent cervical node metastases this type of operation is also indicated even though the mandible itself may not be involved by tumor. In these postirradiation problems where the jaw is not involved the tissues will not tolerate adequate further irradiation and the jaw must be resected simply because it is in the way, there being no other adequate surgical approach compatible with the precepts of cancer surgery. The foregoing concepts apply in all particulars to carcinomas of comparable extent arising in the anterior lateral area including the tonsil and adjacent pharyngeal wall.

It is believed that the considerations outlined here constitute absolute indications for the radical combined surgical attack on intraoral cancer. The relative or controversial indications comprise those clinical problems in which the carcinoma is not so far advanced and in which irradiation techniques are thought to have a chance of salvaging the individual. It may seem that the advanced stages of disease described as absolute indications for surgery are not common. When it is realized that the over-all cure rate of intraoral cancer in the best hands is about 25 per cent it should be apparent that some 75 per cent of patients with this disease go through these advanced stages eventually and at some time in their course they are theoretically still operable and potentially salvageable by such radical surgery. The problem then is to choose the seemingly early cases which is not radio-curable and use surgery primarily. This question can only be answered by continued study of large series of cases so that the range of equivocal indications can be narrowed. It has been demonstrated that the combined operation is technically feasible and offers some hope to patients with advanced intraoral cancer. It remains to apply the procedure to earlier cases in the hope that the over-all cure rate will be increased. If formerly hopeless intraoral cancer can occasionally be salvaged by this technique it seems only logical that the poor cure rate of earlier cases could be improved by application of these radical surgical principles.

Technique of Combined Neck and Jaw Resection—The skin incisions begin with a Kocher type incision curving downward and forward from the mastoid process to the hyoid bone and then upward to the midline of the chin. From the midpoint of this incision another is carried straight downward to the level of the clavicle ending at the lateral border of the clavicular junction of the sternocleidomastoid muscle (Figs 7 8 9 and 10). These incisions are carried through the platysma and then reflected posteriorly to the trapezius, and medially to the sternohyoid muscle or midline. The upper skin flap is dissected back to the level of the alveolar ridge of the mandible, unless the intraoral tumor involves soft parts lateral to the mandible and buccal gutter. The skin flaps particularly the upper, can be varied considerably, depending on the individual problem of primary tumor location and extent.

After the skin flaps are mobilized the neck dissection is begun at the clavicular level and carried upward as a routine radical neck dissection. The tissues of the posterior triangle the sternomastoid and omohyoid muscles, and the internal jugular vein are sectioned and reflected upward to the crossing of the hypoglossal nerve above the carotid bifurcation. The omohyoid is then cut away from the hyoid bone and the anterior portion of the submaxillary dissection is then effected extending the dissection to the symphysis menti. The digastricus and stylohyoid muscles may or may not be sacrificed as the local tumor problem requires. After the submaxillary area is freed from below it is left attached superiorly to the undersurface of the mandible. At this point it is usually best to complete the upper posterior neck dissection cutting across the upper portion of the sternomastoid muscle usually also the tail of the parotid gland and ligating and dividing the upper stump of the internal jugular vein. This portion of the dissection is then carried to a point just anterior to the angle of the mandible leaving the entire neck dissection tissue attached to the undersurface of the horizontal ramus.

The upper neck incision is then extended through the midline of the lower lip into the mouth and the mandible is sectioned in the midline with a Gigli saw. From this point considerable variation may be exercised depending on the site and extent of tumor involvement. If the primary lesion is in the tongue and a hemiglossectomy is necessary the tongue is split in the midline and the excision carried back as far as necessary. If the tumor occupies only the floor of the mouth the tongue is spared. If palate tonsil or pharyngeal wall is involved excision is necessary. The soft palate can be removed at least to the midline. The amount of mandible removed depends on the extent of the tumor but as a general rule the entire hemimandible is removed if the bone is invaded by cancer or if the lesion is posterior in the floor of the mouth gingiva buccal mucosa or palate. If the bone is not invaded and the lesion is fairly well anterior it is our belief that only the horizontal ramus need be removed. Preservation of the ascending ramus allows much better restoration by bone graft or prosthesis at a later date. After all condemned intraoral soft tissue is freed by incision the mandible is then either disarticulated or sectioned at the indicated level and the surgical specimen consisting of the cervical dissection jaw portion and intraoral tumor, is removed in one piece.

all our recurrences with one exception were apparent within ten months and averaged five months. The one exception had recurrence in the twelfth month.

Indications for the Operation of Combined Neck and Jaw Resections—At the present time we consider the indications for this type of procedure to be in two categories: the absolute and the relative. The absolute indications would consist of clinical situations where squamous-cell carcinoma of the buccal mucosa, gingiva, or floor of the mouth has invaded the mandible by direct extension and has produced cervical node metastases. There is no way to salvage such a patient other than by radical neck dissection, excision of the hemimandible, and radical excision of the involved soft parts all in continuity. Adenocarcinoma or mucocutaneous carcinoma of the major or intraoral minor salivary glands can produce the same anatomic problem. Another absolute indication is postirradiation recurrence or persistence of cancer involving soft tissues adjacent to the mandible, whether or not the jaw is involved, and whether or not cervical node metastasis is evident. For extensive tongue lesions recurrent after irradiation with or without clinically apparent cervical node metastases this type of operation is also indicated even though the mandible itself may not be involved by tumor. In these postirradiation problems where the jaw is not involved the tissues will not tolerate adequate further irradiation and the jaw must be resected simply because it is in the way; there being no other adequate surgical approach compatible with the precepts of cancer surgery. The foregoing concepts apply in all particulars to carcinomas of comparable extent arising in the anterior palatal area, including the tonsil and adjacent pharyngeal wall.

It is believed that the considerations outlined here constitute absolute indications for the radical combined surgical attack on intraoral cancer. The relative or controversial indications comprise those clinical problems in which the carcinoma is not as far advanced and in which irradiation techniques are thought to have a chance of salvaging the individual. It may seem that the advanced stages of disease described as absolute indications for surgery are not common. When it is realized that the over-all cure rate of intraoral cancer in the best hands is about 25 per cent, it should be apparent that some 75 per cent of patients with this disease go through these advanced stages eventually and at some time in their course they are theoretically still operable and potentially salvageable by such radical surgery. The problem then is to choose the seemingly early cases which is not radio-curable and use surgery primarily. This question can only be answered by continued study of large series of cases so that the margin of equivocal indications can be narrowed. It has been demonstrated that the combined operation is technically feasible and offers some hope to patients with advanced intraoral cancer. It remains to apply the procedure to earlier cases in the hope that the over-all cure rate will be increased. If formerly hopeless intraoral cancer can occasionally be salvaged by this technique it seems only logical that the poor cure rate of earlier cases could be improved by application of these radical surgical principles.

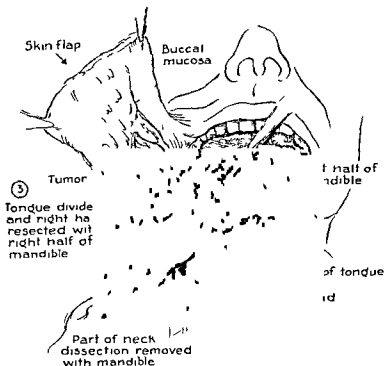


Fig 9

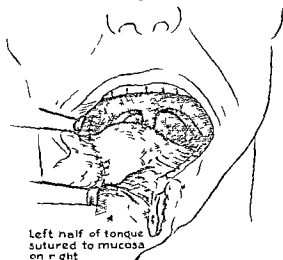


Fig 10

Figs 9 and 10.—Diagrammatic presentation of the operation of combined jaw and neck dissection.

In Fig 9 the upper inset shows the usual skin incision. The lower drawing shows the intraoral soft part incisions that can be utilized in the situation illustrated.

Fig 9 illustrates the first stage of the operation as the neck dissection is completed. In the drawing the upper or cheek flap is raised to an exaggerated degree only for purposes of anatomic demonstration.

Fig 10 illustrates the operative procedure after section of the mandible and incision through the midline of the tongue. Hemiglossectomy of course is performed only if the tongue is involved by the tumor; otherwise, it is spared. After this stage the mandible is disarticulated or sectioned posteriorly at the required level.

Fig 10 illustrates the primary step in closure: suture of the medial cut edge of the intraoral soft parts to the buccal mucosa lining the cheek flap. If a partial glossectomy has been done as shown here, the tip of the tongue should be left free if possible and the tip reconstructed by sutures. This will greatly facilitate tongue function and improve the linguals in speaking.

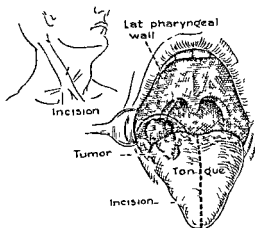


Fig. 7

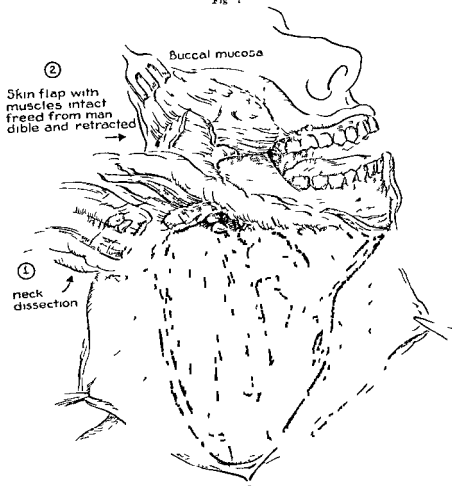


Fig. 8

(Opposite page 519)

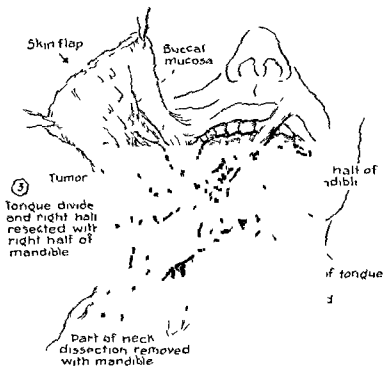


Fig 9

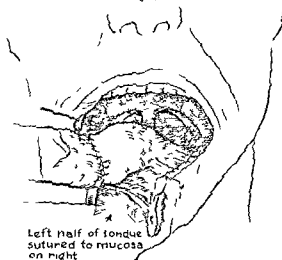


Fig 10

Figs 7 & 9 and 10—Diagrammatic presentation of the operation of combined jaw and neck dissection

In Fig 7 the upper lip is shown

Intraoral so

Fig 8

drawing the

tongue down

Fig 9, shows the operative procedure after section of the mandible and the midline of the tongue is shown

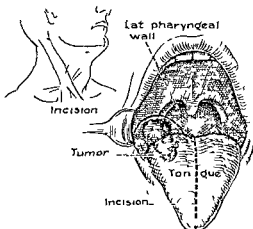


Fig. 7

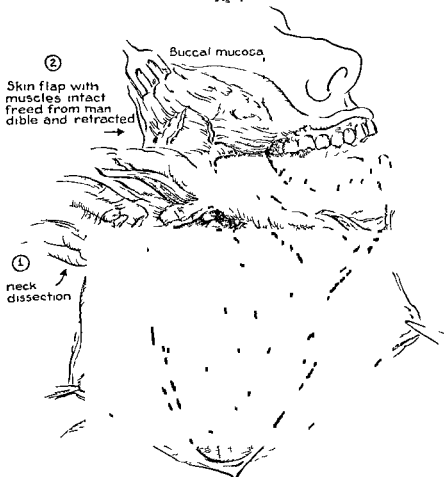


Fig. 8

(For legends see opposite page)

Reconstruction is accomplished by suturing the medial cut edge of the oral mucosa whether it be remaining floor of mouth or sectioned portion of tongue to the buccal mucosa lining the upper skin flap. This reconstitutes the oral cavity and isolates the mouth from the cervical dissection area. Careful technique here with double layer interrupted suture line will usually result in a watertight closure and primary healing. The frequent problem, however, of having to work with irradiated tissues may result in a breakdown of healing and resultant oral fistula. Such a contingency is of minor importance in the neck as compared with a leak in an intraperitoneal bowel closure. After the mouth closure is effected the skin flaps are approximated with two or more Penrose drains strategically placed. A tracheostomy is then performed if it has not already been done.

DISCUSSION

Two separate problems have been presented in this study of our experience in resection of the mandible for neoplastic disease. The surgical treatment of tumors primary in the jaw is an entirely different exercise than the resection of this bone in the surgical attack on advanced intraoral cancer. In the latter situation the mandible is simply a portion of the en bloc resection which includes the intraoral primary tumor, the regional lymph nodes and the intervening lymphatics. In this respect the mandible is implicated in three ways: it may be infiltrated by cancer by direct extension, its periosteum through which passes a large portion of the lymphatic channels from the gingiva, buccal mucosa and floor of mouth may be closely associated with the primary cervical metastatic lesions, the jawbone may simply be a structural barrier to surgical access to intraoral cancer from any direction, and an architectural obstruction to soft tissue repair.

This last consideration has been one of the main obstacles in acceptance of resection of the mandible for intraoral cancer, particularly when the bone itself is not directly invaded. The resultant cosmetic and functional defects have been greatly exaggerated in the minds of those surgeons who have neither performed such an operation nor personally followed the victims of intraoral cancer to their death. There is no more cruel death than that from head and neck cancer, the distribution of sensory end organs in the body being in all respects what it is. The problem of plastic reconstruction of these patients is important but it is secondary to the problem of curing cancer. Our patients have invariably been grateful and those who had recurrence after such surgery have had significant palliation.

The degree of palliation achieved by radical surgery in advanced intraoral cancer has been an unexpected dividend. It is chiefly due to interruption of the cervical plexus and third division of the fifth cranial nerve plus the removal of ulcerating infected and frequently necrotic cancer in the mouth.

As yet there has been no difficulty in gaining consent of the patient for radical surgery. Most of the patients have been so miserable that they have acceded willingly to any suggestion. When the operation of combined neck and jaw dissection is applied to patients with relatively early lesions as long



Fig 11



Fig 12

remained well to date

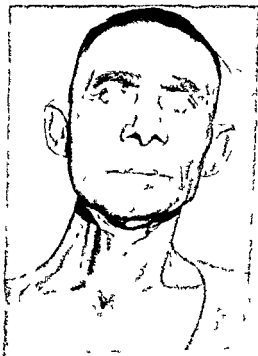


Fig 13—Postoperative appearance of 63 year old man who was operated upon in January 1945 for a recurrent cancer of the palate involving the jaw and with cervical node metastases fixed to the mandible. There was radionecrosis of the intral soft tissues and trismus so complete that nutrition was poor. A combined soft part jaw and radical neck dissection was performed. Note minimal cosmetic defect. He has remained well to date twenty months after surgery and has been working at his usual job.

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ically it should be, such recommendations must be based on more critical evaluation than is possible at the present time.

Restoration of normal functions and symmetry after a combined neck and jaw dissection is not as urgent a problem as it might seem. The primary repair results in a functional state which is not only compatible with maintenance of nutrition but usually allows weight gain and recovery to a normal condition. Our surviving patients have all been improved by the operation and all but two have refused bone graft restoration. It is our impression at the present time that the plastic reconstruction of these patients is entirely secondary to the problem of eliminating cancer. Procedures for reconstruction of the jaw such as primary bone graft, or the insertion of steel or Vitallium bars, compound an already complicated problem in healing and may obscure recurrence of cancer during the follow up period. This last is not actually very important because when cancer recurs after a combined neck and jaw dissection there is of course, little or nothing that can be done further toward cure. Another obstacle to immediate attempts at restoration of bone continuity is the hazard of working with irradiated tissues. Most of our cases having radical surgery have had prior irradiation to an extent that healing of the surgical repair is embarrassed. In a contaminated field and working with radiation damaged tissues we have hesitated to add a foreign body to the already difficult problem of tissue repair.

Most patients with intraoral cancer are in age groups in which function is paramount to appearance. So far it is our experience that a dental prosthesis is the most practical compromise for those patients who have had a resection of one half of the lower jaw. Many of these individuals are content to leave well enough alone and will not bother with prosthetic dentures. It is not our purpose to minimize the importance of plastic reconstruction but rather to assign it a proper place in relation to cancer.

SUMMARY

A review of our experience in tumor surgery of the jaw has been presented. It is apparent from this study that tumors arising from the bone itself are in the minority. The major considerations at present are secondary involvement of the bone by intraoral cancer arising in the soft tissues and the newer concepts of surgical attack on intraoral cancer which require excision of part or all of the hemimandible whether or not it is directly invaded by tumor. The operation of combined neck and jaw dissection is described and an interim evaluation of it is presented.

REFERENCES

1. Martin Hayes E. Personal communication.
2. Pack, G. T., Scharnagel I. and Wolff M. Principles of Excision and Dissection in Continuity for Primary and Metastatic Melanoma of Skin, *SURGERY* 17: 849-866, 1945.
3. Ward, Grant. Presented before the James F. King Society, New York N. Y. Jan. 15, 1949.

QUARTRECTOMY—ITS APPLICATION IN MALIGNANT MELANOMA

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MALIGNANT melanoma has achieved a reputation among surgeons for being one of the most hopeless of malignant tumors, which has resulted in a spirit of defeatism permeating the minds of the professional public. While it deserves a place in the scope of serious malignant disorders it remains that it is much more amenable to therapy than, for instance, carcinoma of the stomach and lung—its reported five year cure rate averaging about 20 to 25 per cent¹ where in the case of the stomach and the lung the rate is much lower—5 to 10 per cent at best. Also the lesion is most often located in a position where it can be observed, diagnosed earlier, its extensions and metastases are more accurately established, and the application of radical surgery with wide margins more definitely accomplished. Therefore the modern idea of hopelessness is not a justified concept.

The problem today is simply to learn why surgery has not in a malignant tumor so susceptible to radical treatment elevated the survival rate of these patients. The truth can be learned only by a study of our past experience in the treatment of this condition, sifting out possible defects of our therapy and attempting to correct what we may be doing that is wrong. It is irritatingly tantalizing to view these tumors so far removed from vital structures at their conception and realize that with our present methods we can not arrive at a better survival rate. They arise in the skin, its appendages or some epithelial structure not so obscure. The medical profession has learned the danger of the black mole, its growth and extensions, and is seeking the aid of the surgeon much more rapidly. If surgery is a proper method to cure this disease surgeons have not demonstrated their ability to achieve good results. Radical surgery has proved its place in the most successful of procedures to rid the body of malignant disease and until some superior chemical, electrical or biologic method is evolved must be employed if we wish to better our results. Some of the defeatism exists in the fact that radical surgery has been employed when the condition is far beyond any aid surgery could possibly afford.

Melanoma demonstrates one of the characteristics of malignancy beautifully, namely the fulminating and the nonfulminating nature of the tumor. Pathologically one cannot prognose which melanoma will be a fast killer and which one is slow growing, or nonfulminating. Figs 1 and 2 clearly demonstrate this fact. The histologic structure of Fig. 1 appears to be a much more rapidly growing tumor than that in Fig. 2 but the first patient lived one year

¹Robb led with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the author.

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and nine months after the onset whereas the second patient lived a period of only four months. The criterion that has appeared to be significant in the 33 patients seen at Kennedy Hospital in the past two and one half years has been the rate of growth observed by the patient and his physicians, which has been obtained in the history. This has proved most reliable in every

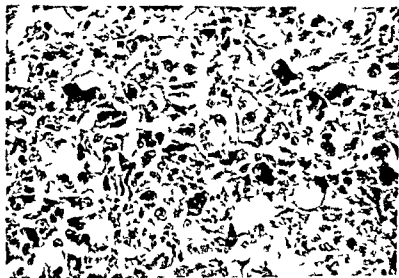


Fig 1—Picture of a rapid growing melanoma. Patient survived one and three quarters years.



Fig 2—Relatively benign looking histologic picture of a melanoma. Patient survived four months.

instance with the possible exception of those arising in the eye. Advanced age of the patient appears to be a retarding influence on the growth but can not be relied upon in many patients. Another observation about fulmination exists in the known slow growing melanoma. We have observed several with a history of slow growth, apparently responding to surgical treatment, and suddenly, after appearing to be under control for a period of as much as four years become fulminating with rapid fatal spread in the course of a few months. In this respect the incidents suggest that the natural course of the tumor or surgery itself has been a dam which successfully controlled the flood water up to a certain period when the dam finally and precipitously gives away.

In reviewing our cases it appears that our surgical efforts in this fulminating group or in the group which after a period of relative benignity assume the fulminating role have been futile. Not a single case has shown a favorable response to surgery and when this fulminating characteristic is manifested beyond a question of doubt we do not employ surgery in these cases. For instance a 20 year old patient entered the hospital with a large mass of involved glands in the right groin subsequent to his observation that a mole appeared at the lower portion of the right thigh. The time element from first recognition until hospital admission was three months. He was anemic, cachectic and weak. A ray examination failed to reveal metastases. No nodules were noticed elsewhere. Ordinarily we would have performed hemipelvectomy with dispatch once the melanoma was verified by histologic study. After one week's observation the groin masses enlarged rapidly, could be felt along the iliac vessels by rectal palpation and his general condition became worse. His family insisted upon taking the patient to his home when informed of the fulminating surgically hopeless condition where he died three weeks later exactly four months from the time of onset. It is our contention that in a case of this sort surgery is futile and should not be employed. We hesitate, of course to admit it but surgery in this type of case fails and a simple study of the details of the history tells us why. The case histories which follow demonstrate the indication for treatment of the slow growing melanomas and need not be repeated here. There are no reports from any source which have suggested any degree of favorable response in this type of fulminating case. As soon as the nonfulmination of the case is established we must then turn to the type of treatment which is most efficacious.

In seeking the type of treatment one is striving for a method that will produce as good results as the ophthalmologists have achieved in melanoma arising in the eye. The early lesions are simply treated by enucleation which effects 90 per cent five year survival rate. When the periocular space is invaded however exenteration effects a five year cure rate of 20 to 30 per cent exactly the same figure pertaining general surgical experience. Callender¹⁴ has attempted to parallel prognosis with the pathologic picture and after the examination of 500 melanomatous eyes believes that there are four types and that longevity depends upon the pathologic type. There is also disagreement

amongst pathologists in respect to eye melanoma. Some believe it is a different tumor from melanoma located elsewhere in the body. Others vigorously declare that these eye tumors are the same as those existing in other parts. However, the facts suggest that when melanoma arises in the eye at a site which impairs vision, consultation is prompt and definitive operation is performed much earlier than in the general surgical lesions and when the melanoma arises at a site which does not affect vision the operation is tragically delayed and the results then compare with the general surgical experience. This presupposes that with early recognition of a limb body or head melanoma wide local excision should suffice to achieve the excellent rate obtained by the eye surgeons. This, unfortunately, is not true.

A brief perusal of the various methods of surgical procedures is in order.

Preventive Surgery—This method has been employed for years heralded by explosive propaganda and has resulted in a scramble for the urgent removal of moles after a lecture heard by students nurses laity and physicians. After a while the panic disappears and the moles are regarded nonchalantly. Blood good² removed and studied 300 moles none of which were malignant. He believed however that he could predict which moles would become malignant and therefore which ones should be removed. Each person averages 20 to 30 moles some have greater numbers but when multiplied by the number of people in the world there must be in the neighborhood of 10 to 40 billion moles in the world population. The number that are or become malignant must be infinitesimally small compared to the total number. A demoling of the population is therefore impractical. Ackerman³ has stated the generalities about the relation of moles to malignancy in a practical manner. He comments upon the general benignity of the raised brown mole and the hairy mole that moles above the umbilicus are less dangerous than those below it that the dorsum of the foot is a very dangerous place for a black mole that moles in sites of frequent irritation are vulnerable etc. and one can gain from his dicta a sensible approach to the problem. The deeply pigmented mole in the child will usually not be dangerous until after the age of puberty. One point is clear. It is not known how many melanomas are aborted by preventive mole removals if any although oncologists and propagandists intimate triumphant results by this maneuver. Nevertheless preventive removal should not be unduly discouraged. It is an interesting sidelight in 1949 to recognize the castration leveled at the surgeon dermatologist and early oncologists when melanoma seemed to sprout following the removal of a mole. We now know that these moles were malignant before removal or partial extirpation.

Local Excision—There is little need for comment about the procedure of local excision. Melanomas have been excised locally with or without great margin with uniformly poor results. Surgeons are well aware of the defects of this method because it was the earliest method employed and today one sees patients who have had local excision due to improper diagnosis and inexperience of the operator. All competent students of this disease con-

demon local excision because of its known failures. However, several of our patients survived three to four years after local removal before extensions or metastases appeared. In these cases melanoma was found thriving at or near the original site as well as in the distant metastatic areas. Reflection about the course of these cases suggests that these particular tumors were nonfulminating and the experiences may afford a clue to the proper treatment. To us it means that if an extremely radical procedure had been employed at the time of the original operation instead of local excision, not only five year survival but permanent cure may have been established. This last statement is actually the concept upon which basis quarterectomy is favorably considered in the treatment of this disease.

Local Excision Plus Regional Glandular Dissection—A method now commonly used consists of removal of the local lesion widely and deeply repairing the local defect by grafting and at a later date supposedly allowing enough time for the malignant cells in the lymphatics to reach and be trapped in the regional glands. radical regional glandular dissection is performed.

To illustrate a 55 year old man appeared with a small melanoma of the scalp in the right temporal region of seven months duration. The lesion grew slowly and became ulcerated. No palpable cervical glands were present.

Operation was a radical excision with a skin graft to the area. Three weeks later a radical gland dissection of the right side of the neck was done. No melanoma was found in any cervical nodes.

This seems to be a proper operation for a lesion in this site. The lymphatic drainage is possible through the channel anterior as well as posterior to the ear. Total excision of the channel is not practical and of course amputation cannot be done. Unfortunately this procedure does not show much improvement over local wide excision but Ackerman³ stated that the results of this type of surgery suggest about 35 per cent five year survival in a small group of selected cases which is better than the original 25 per cent. Unquestionably it is suggested that if this procedure is employed very early in a nonfulminating case one may expect better than the existing survival rate. The great disadvantage of this operation exists in the fact that one cannot totally extirpate the disease along with its lymphatic drainage without cutting across the lymphatics or traumatizing the nodes which may contain microscopic foci of the neoplasm. Therefore this operation is proper only when the more radical approach is not allowable.

Local Excision Plus Removal of the Lymphatic Drainage Tract and Its Regional Glands—The method of local excision plus removal of the lymphatic drainage tract and its regional glands sprung from Handley,⁴ polished and highly advocated by Pringle,⁵ and popularized much later by Park⁶ and a few others. It is more radical than the previous procedures and one can begin to notice perhaps longer survival by this method but the results are not so convincingly good that one does not question the use of a more radical procedure. Not enough cases have been observed for long periods to be certain of its efficacy.

The procedure is best illustrated by report of a 34 year old man who recognized an abnormal black mole on the inner surface of the right thigh. It was present four months when an experienced surgeon recognized the tragic importance and transferred the patient to Walter Reed General Hospital promptly. Two days later the thigh and groin were prepared and draped. The tumor was removed with a two inch margin from its borders and deeply enough to include the fascia lata. Microscopic study confirmed our suspicions of the malignancy of this melanoma. Consequently a wide tract of skin, subcutaneous tissue and fascia were excised in continuity. The procedure extended from the local site upward with radical removal of the femoral inguinal and iliac nodes to a site well above the hypogastric artery, removing with the mass the femoral vein. It was necessary to incise Poupert's ligament to gain proper exposure. No melanoma could be demonstrated in the excised glands. The patient is free of demonstrable disease by a thorough metastatic survey done at Kennedy Hospital three years and four months post operatively.

In another case, similar to the Walter Reed case the patient has survived three years and five months without noticeable disease. This Handley procedure certainly is the method of choice for melanoma of the trunk. Iack has performed the operation on several patients whose lesions resided in the axillary line about the level of the umbilicus. In these instances he has dissected the axilla, groin and wide tract containing the tumor and its likely lymphatic channels in continuity and in one stage. It has the disadvantages of cutting across possibly involved lymphatic channels and of traumatizing by manipulation the nodes bearing microscopic foci. However this operation better fulfills the idea of radical surgery than the other procedures.

Amputation With or Without Regional Glandular Resection—High thigh or arm amputation has been utilized in the past more than we realize and it has notably failed except in one instance namely the more favorable subungual melanoma. The slow course and relative benignity of melanomas which arise under the finger or toe nails are well recognized. Many reports of long survival in this group indicate that a proper method may be local tie or finger amputation, followed by regional gland dissection. In these subungual cases more radical procedures are not indicated with our present knowledge unless disease is discovered in the limb in the postoperative studies. For melanoma of the dorsum of the foot, leg or thigh ordinary thigh amputation with or without gland dissection is to be condemned. I remember a case where amputation was performed for melanoma of the dorsum of the foot of short duration. Groin dissection was performed shortly after the amputation. The patient returned to the Cincinnati General Hospital four and one half months after the amputation with large clusters of melanomatous tumor residing in the amputation incision. Obviously melanoma cells must have been present in the lymphatics at the time these channels were incised during the amputation and once seeded in the tissues of the stump thrived vigorously. Other cases of amputation in similar sites revealed glandular

involvement or distant metastases in short periods of time following operation

When these considerations are perused pessimism can be lifted only if more radical early surgery can be evolved. The prominent factors in more radical surgery demand an operation that will in one sweep remove the local lesion, all of its lymphatic vessels and the barrier nodal drainage without manipulation of the lesion its tracts or barrier. Melanoma teaches the surgeon better than any other malignant tumor not to traumatize or manipulate the tumor because these acts may inevitably result in malignant spread. Holman has stressed this point in student examination of the cancerous breast. I performed radical neck dissections upon two patients with melanoma of the face who had been subjected to aspiration biopsies of involved nodes approximately ten days prior to operation. Great astonishment was manifested by all who examined the resected material when it was observed that a black path existed between the aspirated gland and the point on the skin where the needle was inserted. These paths demonstrated the presence of malignant cells when examined microscopically.

To meet the demands of this radical approach quarterectomy seems adequately to fulfill the principles. This means interscapular amputation of the arm and hemipelvectomy for the leg cases. These are mutilating procedures not desirable and would be tragic unless employed for the saving of life when no other procedures will suffice. Properly employed the procedure does not include the operator's manipulating the tract or nodal barrier. The virtue of this type of operation lies in the fact that the nodal area is resected radically en bloc with the lymphatic pathways and local site. These radical amputations are accepted by the profession for other malignant tumors especially osteogenic fibrosarcomas and neurosarcomas but have not been employed for early melanomas. Pack⁸ has advocated hip joint disarticulation combined with regional gland dissections in some selected cases of melanoma of the thigh, but mainly when he did not feel that exersion in continuity was feasible. He has not advocated this radical procedure in the early case. Hip joint disarticulation and gland dissection does not meet the degree of thorough radical surgery that this malignant tumor requires. First because the incision encircles the upper part of the thigh which necessitates cutting across involved lymphatics entering the nodal barrier. Second the nodal barrier is manipulated and this coexistent trauma to involved glands may dangerously effect a spread of the tumor. Third it does not permit resection of the iliac nodes without undesirable manipulation. Fourth the incision is directed in the fibers of Poupart's ligament which is too close to the nodal barrier for radical surgical comfort. Last hip disarticulation in itself is a mutilating procedure not much more mutilating than hemipelvectomy. It has one advantage only over hemipelvectomy that it allows a poorly functioning prosthesis which is impossible to date follow in hemipelvectomy. Pack¹⁰ stated in one article that he performed hemipelvectomy in two cases of melanoma but the details of the cases are not given.

The incision I employ in hemipelvectomy for melanoma begins anteriorly above the iliac crest and extends to the pubis in a semicircular fashion which

includes approximately three inches of skin and subcutaneous tissue above Poupart's ligament. A deeper incision in the muscle layer includes a transection of the muscles approximately three inches above Poupart's ligament. Peritoneum is reflected medially. If there are no involved nodes above the hypogastric artery the external iliac artery is ligated and the remainder of the anterior work accomplished before the iliac vein is tied. The iliac artery and vein are transected just below the hypogastric artery and the nodes and areolar tissue below this point are not dissected but are removed with the resected quarter. Therefore, the nodal and lymphatic channels are amputated at a distance well above the femoral regions without any manipulation of the tissues in that vicinity. We, therefore, felt justified in advising quarterectomy for melanomas early, preferably before the main nodal barrier became involved and have employed the procedure in four cases three involving the leg and one the arm. The postoperative period is not long enough to be suggestive but the rarity of the tumors requires that several clinics study the results in quarterectomy so that significant data can be collected. The gross findings of the resected quarters constitute evidence which may predict more favorable outcomes than we have observed by less radical methods.

Preoperative Studies—These are extremely important because the mutilation would not be justified except in those cases where after thorough study it is believed that the disease has not progressed beyond the nodal area available for resection. It involves thorough history and physical examination which searches for glandular involvement and subcutaneous nodules from the top of the head to the toes. If any suspicious nodules are observed removal and histologic study must be performed. X-ray examination of skull chest spine and long bones must be included in the study. These studies require only a few days and should be completed with dispatch. One is always aware of the possibility of blood stream spread and there is no accurate method of determining this at any one period unless the history of fulmination is at hand. Melanin in the urine or blood is not an accurate indication of metastases. For instance we have seen melanuria in a favorable case where the extensively involved case with widespread metastases may not reveal the presence of the melanin in the urine. We have also observed that in a given case melanuria is likely to be intermittent and its existence is therefore of doubtful significance. However if a case seems to be a favorable one procrastination about the possibility of blood stream spread is unimportant because if that type of spread has unknowingly already occurred quarterectomy will not materially add to the patient's dilemma because his life span will not be long. Also mentally it may benefit the patient to know that a definite radical procedure has been performed in his behalf.

The important gesture in the preoperative studies is the biopsy and the manner in which it is obtained. Once the patient enters the hospital the patient nurses attendants and inexperienced surgeons are warned about trauma to the lesion or its lymphatic involvements. We consider the biopsy of major importance. If melanoma is seriously considered the local lesion is excised in

toto with a large margin in all directions and the resultant defect immediately skin grafted. Unfortunately, most of our patients have been "cut into" before arrival at the hospital and this trauma has not been avoided. Two or three days later when the pathologist is certain of the malignancy the radical procedure is performed. It is our belief that a cardinal sin would be to incise or remove an involved lymph gland unless that is absolutely necessary. If the local lesion has been removed previously or the enlarged glands are the result of gastrointestinal melanoma then glandular biopsy may be in order but in all five cases presented here the local lesion gave the answer, and the glands were not traumatized except in the last case and that had been done prior to admission to Kennedy Hospital. Until we are more confident as we obtain experience in this radical procedure we prefer not to perform quarterectomy from frozen section alone although that may ultimately be the procedure of choice. One reason is the effect upon the patient. It is difficult for a patient to grasp the seriousness of the situation at first. The permanent histologic study has aided this phase of the problem because the patient is aware of the fact that the positive information obtained is trustworthy in all respects has grasped the enthusiasm for radical surgery and feels resignedly hopeful.



Fig 3 (Case 1)—Amputated quarter note heel lesion

MELANOMA CASES

CASE 1—J H M was a 59 year old diabetic patient. This arteriosclerotic white man was admitted to Kennedy Hospital April 7, 1948 complaining of an ulcer on the right heel of five month duration. The black ulcer gradually became larger but was not painful. There was a small mass in the right femoral region. Biopsy revealed melanoma. After regulation of the diabetes right hemipelvectomy was performed on April 19, 1948. There was moderate shock but the patient tolerated the procedure well. There was wound infection and lough of the muscles in the posterior flap. This responded to local therapy although

a draining sinus is still present. Seventy-nine days after operation, homologous serum jaundice appeared from which the patient promptly recovered. Examination of the resected quarter revealed melanoma of the heel, with metastatic involvement to the right femoral nodes. Lymph nodes above the femoral region were enlarged, but were free of malignancy, demonstrating only lymphoid hyperplasia upon pathological study. He remained in the hospital for a period of five months. X-ray examinations of pelvis and chest were made at regular intervals but there was no evidence of metastases.

Follow up Study—Ten months postoperatively, draining sinus persisted. There was no evidence of melanoma in the flap. There were no metastases. The patient was residing in a domiciliary home.



Fig. 4 (Case 1).—Clasp elevated only involved nodes in amputated quarter.

CASE 2—J. T. J., a 30-year-old white man, was admitted to Kennedy Hospital Sept. 17, 1948. He had noticed a small red sore on the anterior aspect of his right ankle for a period of two and one-half years. It progressively increased in size, was asymptomatic except for slight bleeding when it was injured. A local surgeon removed the lesion two weeks prior to admission and the pathological study proved to be malignant melanoma. There was a heeled incision just above the ankle and a pigmented mass in the right femoral region. Metastatic survey was negative. His right leg was amputated Sept. 22, 1948. The wound healed per primam and he was discharged from the hospital on Nov. 1, 1948. Examination of the resected limb revealed involvement of the lymphatics deep to the muscle locally and one femoral node was involved in the malignant process. There was no enlargement of lymph nodes in the iliac region.

Follow up Study—Six months postoperatively there was no evidence of melanoma in the flap. There were no metastases.

CASE 3—T. M. B., a 53-year-old white man, entered the hospital in January 1948 for the treatment of a mass which had appeared in the left axilla and rapidly grew to the size of a grapefruit. Four years previously he had had a mole removed from the posterior axillary region. The small scar from this healed incision was widely excised and microscopic study



FIG 5 (Case 1) —Local lesion just above ankle



Fig 6 (Case 1) —Arrow point to inguinal node. Hic vein has been ligated approximately two inches above Poupart's ligament

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Follow up Study—Six months postoperatively there was no evidence of melanoma in the flap. There were no metastases.

CASE 3—T. M. B., a 33-year-old white man, entered the hospital in January, 1948, for the treatment of a mass which had appeared in the left axilla and rapidly grew to the size of a grapefruit. Four years previously he had had a mole removed from the left parascapular region. The small scar from this healed incision was widely excised and microscopically study



Fig 5 (Case 2) —Local lesion just above ankle



Fig 6 (Case 2) —Arrow points to single involved node, iliac vein has been ligated approximately two inches above Poupart ligament

proved the presence of melanoma in the scar, although it was not possible to know this from clinical examination. Interscapular amputation of the left arm, was performed Feb 27, 1948, after a period of ineffectual radiation therapy had been done at the patient's request. The wound healed per primam and the patient was discharged March 12, 1948. He returned to the hospital in October, 1948 when an examination of the operative region showed it to be free of disease. There were several enlarged lymph nodes in the opposite side of the neck. Radical resection of the glands of the right neck and hemithyroidectomy were performed at this time. Study of the amputated member revealed a large conglomerate mass of axillary lymph nodes with melanomatous involvement and the presence of the tumor in the right lobe of the thyroid. He was discharged on Nov 9 1948, with per primam healing in the neck incision but returned promptly because of weakness in the right arm and hand, headache, nausea and vomiting. New nodules were observed in the scalp, left side of the neck in the flaps of the amputation scar, chest and abdomen. Cerebral metastases produced coma and he died Nov 17 1948—five years after the original mole excision, nine months after the interscapular amputation and one month after the radical neck dissection. Autopsy showed widespread metastases to skin, brain, left cervical lymph node, and chest. The amputation flaps were clinically free from nodules until the final dissemination, but no more nodules were present in these flaps than in the scalp.

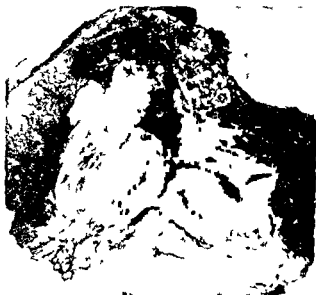


Fig 7 (Case 3)—Interscapulothoracic amputation. Large whitish areas show extensive involvement of nodes.

CASE 4—A 59 year old white man had a mole near the right ankle of one year's duration. The mole bled when struck six months prior to admission. There was a mass in the right groin two and one half months before admission. Metastatic survey was negative. Positive biopsy was done by radical local excision. On Jan 4 1949 an anterior incision was made for proposed hemipelvectomy. When the incision was exposed several large firm, grayish lymph nodes were noticed. Involvement was suspected. Four glands were removed and operation was abandoned. Careful serial studies of the glands failed to show anything but infection. On Jan 10 1949 hemipelvectomy was performed. The wound healed per primam. Epididymitis due to catheter complicated his recovery. The resected limb



Fig 8 (Case 4) —Extensive involvement of nodes in femoral region enlarged nodes above Poirart's ligament show inflammation.



Fig 9 (Case) —Local lesion on the calf recurrent melanoma in scar two years after local removal Quarterectomy not done in this case.

showed that biopsy excision had been total removal. There were many enlarged and involved femoral glands. *Perforating iliac glands* again failed to show the presence of melanoma.

CASE 5—W. C. P., a 24-year-old white man, had a mole removed from the left mid calf region two years before admission. On January 22 he noticed a small mass in the left femoral region while playing basketball. He consulted a physician who incised the gland and noticed the escape of blackish material from the glands. Sections revealed melanoma. He was admitted to Kennedy Hospital on Jan. 26, 1949. The local lesion consisted of a dime-sized scar on the left calf in which were small black areas obviously melanoma. Hemipelvectomy was advised. The patient refused and left the hospital to find a surgeon who could treat the lesion successfully without amputation.

COMMENTS

These cases are believed to be examples of slow growing melanoma. Case 4 may be more fulminating than the rest of the group and the sequence of events in the arm case suggests that after a four-year period, the tumor was now reaching the sudden dissemination stage.

Two patients (Cases 3 and 5) underwent local minor surgery for their malignant moles four and two years, respectively, before glandular metastases appeared. Both had melanomatous involvement of the scars when admitted to Kennedy Hospital. These findings suggest that local surgery, incomplete as it was, had no effect upon the ultimate fate of the tumor and that the long periods of time between local excision and metastases can be attributed to the natural slow growth of the neoplasm rather than to triumphant success due to surgical excision. Also it is suggested that the trauma of the local lesion in these two cases certainly did not contribute to metastatic involvement.

Case 2 demonstrates what may be false security when one relies upon excision in continuity operation because the lymphatics lying deep in the muscles of the calf contained melanoma cells. These lymphatics would not have been effectively removed by any operation short of ablation. The arm case demonstrates that with quarterectomy spreading metastases in the skin flaps did not occur until subcutaneous nodular involvement appeared simultaneously in many other parts of the body. We had treated a similar case by radical axillary dissection. Three months following operation the patient returned to the hospital with widespread metastases of the skin flaps. This latter patient had refused interscapulothoracic amputation. In all of the amputated limbs thorough search of the tissues failed to reveal the presence of melanoma above the femoral nodes. Case 4 demonstrates the difficulty in establishing this fact and the simplicity with which it is solved. When the iliac nodes were noted to be suspiciously enlarged during the first operation the anterior wound was closed and enough time was allowed for the pathologist to be certain of non-involvement before quarterectomy was accomplished six days later. Obviously if involvement of nodes is present at the level of the hypogastric artery or above it quarterectomy should not be performed because proof is then at hand to establish its futility. It is doubtful that quarterectomy would be a fitting procedure for palliation alone. Finally one is compelled to react favorably to the application of radical surgery in the arm case and the last leg case. If, instead of local excision which was done early in these cases quarterectomy had

been done one cannot escape the conclusion that not only five year survival rates could be obtained in larger numbers of cases but that there should be a fair number of permanent cures in the slow growing cases. This concept must be true or we should abandon radical surgery for malignant tumors. It is an interesting observation to notice that experienced surgeons will vigorously maintain that the "most radical operation possible" should be performed in melanoma cases, yet when the actual working procedures of these same surgeons are surveyed they do not include really radical surgery. In other words, we speak of it but do not do it. Handley, Pringle, Peck and a few others have come closer to it than others. In a recent consultation with a well qualified surgeon concerning an early lesion on the heel this surgeon was horrified when quarterectomy was suggested but stated that he must do a tremendously radical operation locally and he believes that he is doing a radical operation. However when he and the pathologist were queried about prognosis both unhesitatingly and promptly remarked that the patient would die of melanoma. Herein lies the trouble. We cannot expect the public to accept quarterectomy unless the surgeons and pathologists are convinced of its worthiness. It also appears to be wasteful and pointless to continue to bombard the lay public with propaganda about early recognition of malignancy and prompt radical therapy in the early lesion when we actually fail to apply this radical surgery early. Reference has been made earlier in this article to the fact that melanoma is not so hopeless when compared to some other malignant tumors. One major reason exists in the fact that the lesion can be early recognized to reside at the end of a limb a site which permits the most favorable radical surgery. The patient will accept it when we can prove to him that the radical attack is a justifiable one and that instead of talking about it we should do it and not abandon it until such an attack has been proved to be hopeless.

SUMMARY

- 1 Five cases of slow growing melanoma are briefly described.
- 2 The gross findings indicate that quarterectomy is the only procedure which will permit an increase in longevity or possible chance for permanent cure—if done early.
- 3 The few cases which demonstrate longevity are probably due to the slow growing nature of the tumor rather than successful outcomes resulting from the surgical procedures previously employed.
- 4 Three cases were treated by hemipelvectomy and one by interscapulothoracic amputation.
- 5 Follow up studies will be necessary on a large number of cases before justification of these mutilating procedures is established.
- 6 If this type of operation should fail to increase longevity or produce some cures it would then be suggested that surgery is not playing a significant role in the treatment of melanoma.

REFERENCES

- 1 DeWeese, Marion S. Final Result of Treatment of Melanoma. Surgeons Club Meeting Ann Arbor Mich May 1948.

STUDIES IN ACUTE CHOLECYSTITIS

I SURGICAL MANAGEMENT AND RESULTS

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THE value of early surgical intervention in acute cholecystitis has been demonstrated by the excellent results reported by Heuer¹ and Glenn. Surgery is indebted to them for their persistent advocacy of what originally was a radical departure from accepted practice. At the Peter Bent Brigham Hospital the late Professor Elliott Cutler abandoned a policy of extreme conservatism in the treatment of acute cholecystitis in 1935. The advantages of early operation were recognized but because many patients entered the hospital in the late stages of the disease it was felt that early operation in terms of the pathologic process was not always possible. Accordingly, a policy of individual management was outlined whereby an attempt was made to select the optimum time for surgery for each patient.² Under this plan of management it was possible to carry out exploration of the common bile ducts in a large percentage of cases and at the same time reduce the mortality to the same levels reported by the advocates of prompt surgery in every case.³

The present report records the experience of the Peter Bent Brigham Hospital during the years 1941 to 1947 inclusive. The over-all experience with biliary surgery during this period is shown in Table I. It is gratifying to note that the operative mortality in acute cholecystitis is approaching that of elective surgery on the gall bladder and biliary passages.

The operative procedures employed in the 134 patients who came to surgery for acute cholecystitis are shown in Table II. There were 114 cholecystectomies, 50 of which were combined with exploration of the bile ducts without a fatality. Twenty patients (15 per cent) had cholecystostomy performed and 12 of these required a second cholecystostomy after a long interval of freedom from symptoms; these are considered as separate primary procedures. There were 2 deaths. In 12 cases secondary operations were performed after preliminary cholecystostomy, the common duct being explored in 6 of these. There were no deaths in this group. The operative mortality of 1.5 per cent is computed in relation to the number of patients rather than the number of procedures.

In a study of acute cholecystitis the importance of recording all cases, whether medical or surgical, has been emphasized recently by Judd.⁴ It is obvious that if apparently moribund patients are excluded from consideration it is possible to present a favorable surgical mortality without giving a true picture of the disease. During the period of this study, there were 19 cases

¹Read at the meeting of the Society of University Surgeons, San Francisco, Calif., March 4-6, 1949.

TABLE I BILIARY SURGERY*

	CASES	DEATHS	MORTALITY (PER CENT)
Cholelithiasis chronic cholecystitis	513	4	0.8
Acute cholecystitis	134	2	1.5
Total	647	6	0.9

Exclusive of cancer and strictures

TABLE II SURGERY IN ACUTE CHOLECYSTITIS

OPERATION	CASES	DEATHS
<i>Primary</i>		
Cholecystectomy	64	0
Cholecystectomy + CD	50	0
Cholecystostomy	2	2
<i>Secondary</i>		
Cholecystectomy	6	
Cholecystectomy + CD	6	
Total procedures	148	
Total patients	134	2 (1.5%)

of acute cholecystitis in which surgery was not performed. Fifteen patients either refused operation or insisted upon postponing it because of exigencies imposed by the war. In 2 cases surgery was not recommended. Two patients died. Thus, in the entire group of 153 patients there were 4 deaths—an overall mortality of 2.6 per cent.

The age of the patients is shown in Table III. There were no operative deaths in patients under 78 years of age. The 2 patients who died without surgery were 65 and 66 years of age respectively. All of the patients who died entered the hospital over four days after the onset of symptoms. Thus there were no deaths at any age in patients who entered the hospital within forty-eight hours of the onset of symptoms.

TABLE III AGE AND MORTALITY

DECADE	CASES	DEATHS
3rd	11	0
4th	16	0
5th	27	0
6th	37	0
7th	4	2
8th	13	2
9th	2	0
	153	4 (2.6%)

THE INDICATIONS FOR AND CHOICE OF OPERATION

The ideal treatment of acute cholecystitis is early cholecystectomy with exploration of the common bile duct as indicated. This should be the objective in every case regardless of the duration of the disease. Unfortunately, however, difficulty in establishing the diagnosis and the poor condition of many of the patients make the attainment of this ideal well nigh impossible. In our experience a great variety of diseases—acute hepatitis, coronary occlusion or disease of the right kidney—to mention a few—may simulate acute cholecystitis and vice versa. In these situations immediate operation can

hardly be regarded as the procedure of choice. In 26 instances in this series operation was delayed for over forty eight hours because the diagnosis was obscure. It is noteworthy however that in only 4 of these cases had the patient entered the hospital within forty eight hours of the onset of symptoms.

Assuming the diagnosis to be reasonably clear and considering only the condition of the patient, there are four possible courses for the surgeon to choose. The first is prompt definitive surgery as soon as fluid balance has been established, the second is an emergency cholecystostomy as a lifesaving procedure, the third is delay in hopes that by such delay the condition of the patient can be improved and the inflammatory process allowed to subside sufficiently to permit definitive surgery to be performed, the fourth and rarest choice is delay hoping that no operation will be necessary. Reasons for these decisions and the hazards involved are illustrated by our experiences.

The relation between the time of admission and the time of primary operation is shown in Table IV. Definitive surgery was carried out within forty eight hours of admission in 49 patients, the common duct being explored in 30 per cent of them. One half of this group had entered the hospital over forty eight hours after the onset of symptoms. Although the classical clinical findings of acute cholecystitis were present and were confirmed pathologically these patients were not gravely ill. Only 3 of them were jaundiced. The gall bladder was gangrenous in only 1 case and there was no instance of perforation or abscess formation. This is the ideal management of acute cholecystitis. Moreover it is the condition of the patient rather than the mere duration of the disease which is the determining factor in the decision to operate. Finally we do not regard this as an emergency procedure to be performed late at night or under unfavorable circumstances. If the patient is so ill that operation cannot be deferred a few hours cholecystostomy is the procedure of choice.

TABLE IV RELATION BETWEEN TIME OF ADMISSION AND PRIMARY OPERATIVE PROCEDURE

TIME OF OPERATION	TIME OF ADMISSION	
	UNDER 48 HR.	OVER 48 HR.
Early definitive (under 48 hr.)		
Cholecystectomy	15	18
Cholecystectomy + CD	10	6
Emergency cholecystostomy	14	6
Delayed definitive (over 48 hr.)		
Cholecystectomy	12	19
Cholecystectomy + CD	18	16
Late cholecystostomy	0	2
	69	67

Cholecystostomy was performed in 22 cases. Twenty of these were carried out within forty eight hours of admission and in 16 cases the disease was of less than forty eight hours duration at the time the patient arrived at the hospital. In 5 cases cholecystostomy was required by technical difficulties encountered at operation but in the remaining cases it was a planned procedure performed through a small muscle splitting incision under local anesthesia. As a group these patients were by far the sickest in the series. All but 2 were over 50 years of age and 15 were over 60 years. Three were di-

netic, 5 had advanced cardiovascular disease and 3 were jaundiced. In 1 there was a large subhepatic abscess and in 3 there were perforations of the gall bladder. The 2 cases in which cholecystostomy was performed over forty eight hours after admission require an explanation. One was a difficult diagnostic problem and the other was a patient aged 78 years, with comparatively mild cholecystitis in whom it was at first thought operation could be avoided.

The value of cholecystostomy has been emphasized^{2, 3, 6} many times but there is still a tendency to regard it as a compromise operation. We feel that it has a definite and permanent place in the surgeon's armamentarium. It is the procedure of choice in the toxic, elderly or diabetic patient particularly if first seen in the more advanced stages of the disease. Properly executed under local anesthesia cholecystostomy adds nothing to the gravity of the patient's condition and it is unquestionably lifesaving in a majority of these cases. It would probably remain the procedure of choice in 5 to 10 per cent of the cases even if all patients entered the hospital early in the disease.

Whether or not cholecystostomy is to be followed by definitive biliary surgery must be settled as an individual problem in each case. In general it should be regarded as the first step of a two stage procedure. Twelve or two thirds of our patients who survived cholecystostomy had subsequent cholecystectomy and in 6 of these the common duct was explored. However in the aged debilitated or poor risk patient it may be best to postpone cholecystectomy indefinitely provided the patient remains asymptomatic. Under such circumstances a cholecystocholangiogram is done before the patient is discharged in order to demonstrate patency of the cystic duct and to exclude common duct stones.

In 5 of our cases no further surgery was advised after cholecystostomy. Four of these patients have remained asymptomatic for five years. In 2 no follow up data are available. The remaining 2 patients returned to the hospital after intervals of six months and four years respectively with recurrent acute cholecystitis. One of these patients was 52 years old at the time of the first cholecystostomy. Six months later a second cholecystostomy was necessary but because of very advanced coronary artery disease with heart failure further surgery was not considered unwise. She remained comfortable and asymptomatic for eighteen months eventually dying of coronary occlusion. The other patient was 74 years of age at the time of the first cholecystostomy. She lived comfortably for four years, then reentered the hospital with another acute attack of cholecystitis and died of pulmonary embolism after a second cholecystostomy at the age of 78 years.

Definitive surgery was delayed for over forty eight hours after admission to the hospital in 65 cases. Over one half of these patients had entered the hospital forty eight hours or more after admission. Difficulty in establishing the diagnosis and the general condition of the patients were the principal reasons for delay. These patients were not so ill that in emergency cholecystostomy was deemed necessary but on the other hand were not thought to be adequately prepared for operation particularly when exploration of the

common bile duct was contemplated. As might be expected jaundice was present in 30 of the 65 cases.

If one elects to delay surgery the details of management are of considerable importance. The progress of the disease is manifested by the temperature, pulse rate, laboratory data, symptoms, and local physical signs are evaluated at frequent intervals throughout the day and at night in doubtful cases. Fluid balance is established promptly by the parenteral route but fluids and a high carbohydrate and high protein intake are given by mouth if there is no vomiting or distention. Penicillin and vitamin K are administered routinely in appropriate doses. Definite evidence of subsidence of the local inflammatory process and a general improvement in the condition of the patients is a requisite for continued observation. The precise indications for abandoning this course and resorting to cholecystostomy will be presented in another communication.

This plan of management is admittedly hazardous because of the dangers of perforation or abscess formation even when the clinical manifestations of the disease are subsiding. It is our belief, however, that by judicious delay the experienced surgeon is able to prepare many patients for definitive surgery including exploration of the common duct whereas by immediate operation he might be committed to a more limited operation. The morbidity and mortality occasioned by stones left in the common duct make cholecystostomy a desirable objective. The fact that none of the patients in this group died and that common duct exploration was performed in one half of the delayed operations encourages us in this stand.

On the other hand, although as a group the patients in whom surgery was delayed were not as ill as those in whom cholecystostomy was performed, there were many gravely ill patients among them. A critical review of these cases indicates that in several instances an emergency cholecystostomy might have been a wiser choice. Thus 7 patients in this group had local abscesses by the time operation was performed. It is interesting, however, that in all of these cases definitive surgery was completed and that the postoperative course was uncomplicated.

In many instances surgery was postponed for an unduly long time, thus greatly increasing the morbidity. In this connection the time at which surgery was done in relation to the onset of symptoms is interesting (Table 1). It can be seen that over 50 per cent of the operations were performed between the second and twelfth day, a time which many surgeons consider to be a period in which surgery is contraindicated. Reluctance on the part of many of our staff to operate during this period is reflected by the group of 48 patients who were operated upon after the twelfth day. In reviewing these cases it is our feeling that little was gained by the prolonged delay and that frequently the technical procedure was rendered more difficult by the development of dense scar tissue in and around the gall bladder. A clinical and pathologic study of this material which will be presented more fully as a separate communication has convinced us that acute inflammation of the gall bladder does not resolve as is the case with the appendix. Once damaged by acute inflammation

tion, the gall bladder undergoes a slow and progressive fibrosis which makes surgery increasingly difficult with the passage of time. The reason for postponing surgery, therefore, is to improve the general condition of the patient so as to permit a definitive operation to be performed rather than to allow complete resolution of the local inflammatory process. Prolonged delay because of persistent evidence of local inflammation is unwarranted and unprofitable. In our experience it was under such circumstances that local perforations and abscesses developed. Moreover, there must be no gambling in the management of this admittedly controversial group of cases. If there is the slightest doubt about the progress of the case, cholecystostomy should be performed.

TABLE V. DURATION OF DISEASE FROM ONSET TO OPERATION

DAYS	CHOLECYSTECTOMY			TOTAL
	CHOLECYSTECTOMY	+ C.D.	CHOLECYSTOSTOMY	
0 ~	11	4	2	17
2-4	11	7	9	27
4-12	19	16	9	44
12+	23	23	2	48

The rarest decision which the surgeon is called upon to make is to withhold operation in the hope that no surgery will be necessary. The hazards of nonsurgical management of acute cholecystitis are fully appreciated but it is our considered opinion that here again the principle of individualization applies. In exceptional cases the best interests of the patient are served by conservative management. On three occasions in this series this course was elected. One was a woman of 78 years with a recurrent attack after a previous cholecystostomy. This case is described in detail later (Case 4). The other two patients were over 60 years of age and both were enormously obese. One had advanced cardiovascular disease and the other had had a recent abdominoperineal resection for cancer of the rectum with metastases. In both of those instances the cholecystitis subsided promptly and the patients have been asymptomatic for periods of two and three years respectively.

THE INCIDENCE OF COMMON DUCT STONES

The frequency of common duct stones in acute cholecystitis has a direct bearing on the problem particularly if one accepts the principle of delaying operation in the hope of being able to carry out exploration of the bile ducts. In the 134 operative cases in this series the common duct was explored in 56 (42 per cent) (Table VI). In 50 of these the exploration was carried out at the primary operation and in 6 it was done at a second stage following earlier cholecystostomy. Common duct stones were recovered in 50 per cent of the cases explored or 21 per cent of the total number of operative cases. There were no operative deaths. However in 2 cases in which surgery was not performed, duct stones were found at autopsy. In this particular

common duct stones have been found in association with acute cholecystitis in 17 per cent of the cases. This high yield of common duct stones constitutes one of the strongest arguments in favor of the policy of individual management.

TABLE VI. INCIDENCE OF COMMON DUCT STONES IN 148 OPERATIONS ON 134 PATIENTS

	COEXPLORATION	STONES REMOVED	DEATHS
Primary operation	50	10	0
Secondary operation	6	2	0
	56	12	0
Ducts explored 4% of patient Stones removed 11% of patients			

The incidence of jaundice in association with common duct stones is of interest. In the entire series jaundice was encountered 37 times. Thirty-three of these patients had common duct explorations, stones being found in 25. There were 4 jaundiced patients in which the common duct was not explored. Two of these had cholecystostomies only, 1 had a cholecystectomy with aspiration of the bile duct and in 1 no operation was performed but common duct stones were demonstrated at autopsy. In the 8 jaundiced patients in whom negative explorations were performed the degree of jaundice was slight, the icteric index being below 30. Postoperative cholangiograms revealed no calculi. This lends support to the belief that jaundice may occur in acute cholecystitis without stones in the bile ducts. However, until more reliable methods of detecting common duct stones prior to operation become available, jaundice must be considered a principal indication for choledochostomy.

In the absence of jaundice or a history of jaundice, common duct stones were found in 4 cases: 3 times in 23 surgical explorations of the bile ducts and once at autopsy. The large number of negative explorations which were required to avoid overlooking a few stones indicates the need for better methods of demonstrating common duct pathology prior to operation.

DEATHS

The four deaths in this series merit a brief presentation.

CASE 1—A woman aged 61 years entered the hospital on the fifth day of her illness with generalized peritonitis. She had had no previous symptoms of gall bladder disease. The diagnosis of acute cholecystitis was completely missed and was established only at necropsy. She died on the tenth day of her illness. Autopsy revealed a large gall bladder and a large pelvic abscess.

CASE 2—A man aged 55 years entered the hospital on the tenth day of his illness with generalized peritonitis. He had had a large pelvic abscess and left lower lobe pneumonia. He had been known to have a perforated ulcer of the stomach. Autopsy revealed a large gall bladder and a large pelvic abscess. The gall bladder contained a large stone and the common duct was dilated. There was a generalized peritonitis and a large pelvic abscess. The left lower lobe pneumonia and extensive pneumoconiosis were also present.

tion the gall bladder undergoes a slow and progressive fibrosis which makes surgery increasingly difficult with the passage of time. The reason for postponing surgery, therefore, is to improve the general condition of the patient so as to permit a definitive operation to be performed, rather than to allow complete resolution of the local inflammatory process. Prolonged delay because of persistent evidence of local inflammation is unwarranted and unprofitable. In our experience it was under such circumstances that local perforations and abscesses developed. Moreover, there must be no gambling in the management of this admittedly controversial group of cases. If there is the slightest doubt about the progress of the case, cholecystostomy should be performed.

TABLE V DURATION OF DISEASE FROM ONSET TO OPERATION

DAYS	CHOLECYSTECTOMY			TOTAL
	CHOLECYSTECTOMY	+ C.D.	CHOLECYSTOSTOMY	
0-2	11	4	3	17
2-4	11	7	9	27
4-12	10	16	9	44
12+	23	23	2	48

The rarest decision which the surgeon is called upon to make is to withhold operation in the hope that no surgery will be necessary. The hazards of nonsurgical management of acute cholecystitis are fully appreciated but it is our considered opinion that here again the principle of individualization applies. In exceptional cases the best interests of the patient are served by conservative management. On three occasions in this series this course was elected. One was a woman of 78 years with a recurrent attack after a previous cholecystostomy. This case is described in detail later (Case 4). The other two patients were over 60 years of age and both were enormously obese. One had advanced cardiovascular disease and the other had had a recent abdomoperineal resection for cancer of the rectum with metastases. In both of those instances the cholecystitis subsided promptly and the patients have been asymptomatic for periods of two and three years respectively.

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operative and nonoperative cases was 2.6 per cent. The operative mortality was 1.5 per cent. Common duct stones were removed in 21 per cent of the operative cases without a fatality. All of the deaths occurred in patients over 65 years of age who entered the hospital over four days after the onset of symptoms.

The advisability of varying the management of this disease to fit the requirement of the individual patient is reaffirmed. The indications and time of election for surgery are discussed.

REFERENCES

1. Heuer, George J.: The Factors Leading to Death in Operation Upon the Gall Bladder and Bile Duct. *Ann. Surg.* 99: 481, 1934.
2. Glenn, Frank: The Surgical Treatment of Acute Cholecystitis. *SURGERY* 23: 597, 1948.
3. Zollinger, Robert: Acute Cholecystitis. *New England J. Med.* 224: 533, 1941.
4. Zollinger, P. and Cutler, E. C.: The Treatment of Acute Cholecystitis: An Evaluation. *J. A. M. A.* 121: 481, 1933.
5. Judd, E. S., Jr.: Surgical Treatment of Acute Cholecystitis. *Proc. Staff Meet. Mayo Clin.* 23: 14, 1948.
6. Wallace, I. H. and Allen, A. W.: Acute Cholecystitis. *Arch. Surg.* 43: 76, 1941.

CASE 3—A man, aged 79 years, entered the hospital on the tenth day of his illness. He had had no previous symptoms of gall bladder disease. A diagnosis of perforated appendicitis was made and immediate operation performed under general anesthesia. A cholecystostomy was done when the true nature of the disease was recognized. This patient developed a *Wells bacillus septicaemia* and died of generalized sepsis on the twenty second day after operation. Autopsy was refused.

CASE 4—A woman, aged 79 years, who had had a cholecystostomy performed four years before for acute cholecystitis entered the hospital on the fifth day of a recurrent attack. She had been quite well in the interim and did not appear seriously ill. Operation was delayed in the hope that the condition would abate spontaneously. Because of persistence of the attack a cholecystostomy was done on the third hospital day. The patient made an excellent immediate recovery but died suddenly on the fourteenth postoperative day. Autopsy revealed massive pulmonary embolism. There was a single small stone remaining in the gall bladder. No stones were found in the common duct.

These 4 deaths can hardly be ascribed to the policy of individual management. However they amply testify to the gravity of the disease and clearly indicate the necessity for early hospitalization. Moreover 3 of them demonstrate the difficulties in diagnosis which may be encountered. Certainly in 3 of the cases earlier hospitalization might have led to a happier outcome by permitting a correct diagnosis to be made in which case emergency cholecystostomy might have been lifesaving. In Case 4 it might be argued that had a cholecystectomy been performed four years previously after the initial cholecystostomy a more favorable outcome would have been assured. But if the patient had died of pulmonary embolism after an elective cholecystectomy would there not be more grounds for criticism than under the actual circumstances?

CONCLUSIONS

The ideal management of acute cholecystitis is early operation with removal of the gall bladder and exploration of the common bile duct as indicated. In approximately 50 per cent of the cases delay in hospitalization, difficulty in making the diagnosis and the poor general condition of the patients make this too dangerous. Under such circumstances one is faced with the choice of a two stage operation, namely emergency cholecystostomy to be followed later by cholecystectomy or delay in the hope of preparing the patient for a definitive single stage operation. The incidence of common duct stones in acute cholecystitis is sufficiently high so that choledochostomy must be an objective in approximately 15 per cent of the cases. None of the deaths in this series are attributable to this plan of management. However the principal error in this series was a tendency to delay operation too long a time thus greatly lengthening the morbidity and in many instances increasing the technical difficulties of the operation by allowing dense scar tissue to develop in and around the gall bladder. The precise indications for cholecystostomy, the optimum time for delayed surgery and the indications for choledochostomy require further study.

SUMMARY

The experience of the Peter Bent Brigham Hospital with acute cholecystitis during the period 1941 to 1947 is reviewed. The mortality including

operative and nonoperative cases was 26 per cent. The operative mortality was 15 per cent. Common duct stones were removed in 21 per cent of the operative cases without a fatality. All of the deaths occurred in patients over 65 years of age who entered the hospital over four days after the onset of symptoms.

The advisability of varying the management of this disease to fit the requirement of the individual patient is reaffirmed. The indications and time of election for surgery are discussed.

REFERENCES

- 1 Heuer, George J. The Factor Leading to Death in Operations Upon the Gall Bladder and Bile Duct. *Ann Surg*, 99: 881, 1934.
- 2 Cleon, Frank. The Surgical Treatment of Acute Cholecystitis. *Surgey* 23: 397, 1948.
- 3 Zollinger, Robert. Acute Cholecystitis. *New England J Med* 224: 537, 1941.
- 4 Zollinger, R. and Cutler, F. C. The Treatment of Acute Cholecystitis. An Evaluation. *J A M A* 121: 481, 1943.
- 5 Jull, F. S., Jr. Surgical Treatment of Acute Cholecystitis. *Proc Staff Meet Mayo Clin* 23: 142, 1948.
- 6 Wallace, R. H. and Allen, A. W. Acute Cholecystitis. *Arch Surg* 43: 762, 1941.

AN EXPERIMENTAL STUDY OF THE EFFECT OF HEPARIN ON THE LOCAL PATHOLOGY OF BURNS

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IT IS a common clinical observation that the appearance of a burn when first examined does not give an accurate estimate of its final depth at the time the slough of necrotic tissue finally occurs. Leach and co-workers¹ and Moritz and Henriques² have shown that the destruction of epithelium and dermis is directly related to the temperature of the thermal agent and the duration of its application. Associated with this initial insult to the skin there is a variable depth to which the endothelium of the superficial vessels is damaged. Further sludging of blood in these vessels and those of deeper layers, destruction of the red and white blood cells by heat, and occasional thrombosis are also seen. With such vascular pathology existing in direct continuity with the deeper vessels of the dermis and subcutaneous fat, might there not occur an extension of actual thrombosis into the vessels of the deeper, but undestroyed layers of the dermis and subcutaneous tissues?

It was our purpose in this work to study the vascular changes associated with the application of a thermal agent and the progression of these in control and heparinized dogs for a period of seventeen days. We hoped to be able to determine, by a study of sufficient duration, whether the entire loss of tissue resulted from the momentary application of the thermal agent or whether secondary vascular changes were instituted at the same time which would involve later the subjacent vascular channels in such a way as to cause further tissue necrosis or at least delay the reparative processes normally operative. At the same time that the study was carried out to ascertain the foregoing information it was felt of interest also to determine whether application of anticoagulant therapy (heparin) might influence such vascular changes as did occur. Hughes and Dann,³ Moritz,⁴ and Underhill and co-workers⁵ did not find that thrombosis secondary to thermal injury was of any frequency or importance. Pack⁶ however reported that a predisposition to thrombosis exists because of the white blood cell disintegration, venous stasis and the viscosity of blood in the damaged area following burning. He recorded the presence of fibrin thrombi and thrombi from precipitation. The results of our study agree more closely with those of Moritz and others in this regard. A study of these normal reparative processes following thermal damage to the epidermis and dermis, when compared to the speed and effectiveness of these same mechanisms with the addition of heparin therapy, has led to some additional and interesting observations which may have clinical therapeutic significance.

METHOD AND MATERIALS

The burns in this study were obtained by applying, under intra venous pentobarbital sodium anesthesia, heated uniform steel blocks measuring $\frac{1}{2}$ by $\frac{1}{2}$ by 1 inch and weighing 32 grams to the dry, freshly shaved skin of dogs. The blocks were heated in a muffle furnace at 100°C for fifteen minutes, to application removed from the furnace singly and placed end on to the dogs skin for fifteen seconds with the only pressure being the weight of the block itself. Moritz and Henriques³ have demonstrated that any temperature over 70°C for longer than one second would produce trans epidermal necrosis. This temperature and time were evolved after some experimentation to reproduce the frequent human deep dermal burn and resulted in burns that included 40 to 100 per cent of the dermis.

A series of ten dogs was burned by this method. However as considerable variation was encountered a second group of six dogs was burned by heating blocks in boiling water for thirty minutes and applying them to the skin for fifteen seconds as described. These blocks dried in two to three seconds on removal from the boiling water.

Each of these sixteen adult mongrel dogs was given six one half inch square burns on one side of the back. Care was taken not to place the block over underlying bony prominence. Using sterile technique these burns were excised by elliptical incisions in the normal periphery under intravenous pentobarbital sodium anesthesia four twelve twenty four thirty six forty eight and seventy two hours later from eight of the animals and five, seven, eleven, fourteen and seventeen days later from the other eight. The wounds were closed primarily in two layers with interrupted silk and the excised flaps fixed immediately in 10 per cent formalin. As each animal was completely healed it was reburned in an identical fashion in comparable locations on the opposite side of the back and the burns were removed exactly as before. This dog served as his own control. Each dog's burns varied considerably from those of the other dogs depending upon the complexion quality of the skin and thickness of the skin. The burns in a given animal were roughly comparable.

Two hours were permitted to elapse prior to administration of heparin for it was felt that such a time period would correspond roughly to the time before a patient could reach such definitive care. Sodium heparin* (10 mg per kilogram of body weight) was administered intravenously to obtain an immediate effect simultaneously with heparin in Pitkin's menstruum (10 mg per kilogram of body weight) subcutaneously. The usual 5 mg per kilogram dosage for human beings had to be increased to this level before effective levels were maintained for twenty four to thirty six hours. A clotting time of more than twenty minutes was maintained throughout the remainder of the experiment by repeated injection of heparin in Pitkin's menstruum. The three tube Lee White method of clotting time determination was used.

*Sodium heparin was supplied through the courtesy of The Upjohn Co. Kalamazoo, Michigan.

complications to heparin were encountered other than one large hematoma occurring subcutaneously twenty four hours after excision of a burn

RESULTS

The repair mechanisms following injury to the epidermis and dermis by a thermal agent are very interesting and efficient. They follow a fairly definite and consistent pattern namely infiltration of polymorphonuclear leucocytes into the junction of destroyed and unburned skin which leads finally to separation of this slough as an eschar of dead tissue, vascular regeneration with new growth of capillaries from the uninjured tissue up to this junction accompanied by fibroblastic proliferation. This serves the function of a scaffold on which epithelial regrowth may take place and at the same time carries nutrition to the newly formed epithelium.

With all of these mechanisms normally operative healing will proceed to completion if first the burn is small enough so that regrowth from the edges of normal skin may cover the entire injured area or second if the depth of the burn was insufficient to destroy all of the hair follicle epithelium in the lower dermis and subcutaneous tissue. In the latter the regrowth of epithelium will take place from these retained undamaged epithelial rests in the base of the burn. Lastly if the burn is too large for complete coverage by these then this same mechanism will produce a layer of granulation tissue the surface of which is formed by a layer of fibroblastic tissue containing a very rich vascular network of normal capillaries. This makes an ideal bed on which a skin graft may be expected to grow.

Our study corroborates the findings of Hughes and Dunn,¹ which indicated the primary importance of vascular supply and regeneration in the healing process of a burned tissue. It serves to carry to the zone of junction between the destroyed and normal skin the 'shock troops' which must clean up the debris from the primary attack namely the polymorphonuclear leucocytes. It is also the source by which nutrition can reach the newly formed connective tissue and must precede the regrowth of epithelium from the edge or from the base.

Vascular Changes—Hughes and Dunn state that burns are usually fully vascularized by the twelfth to sixteenth day depending on the size of the burn. Vascularization precedes both epithelialization and fibroplasia in the superficial part of the burn while in the deeper tissues the formation of new capillaries and fibroblastic proliferation seem to proceed hand in hand. Approach to the surface of the new dermis is upward between the fascicles of undestroyed dermal collagen.

This study of the vascular changes following deep burns was directed to four areas: (1) the zone in the dermis between the destroyed and normal or unburned dermis, (2) the blood vessels in the subcutaneous fat layer and the hypodermis of Moritz (-) from the normal tissue at the periphery of the excised burn and (3) the vessels in the platysma muscle and subjacent to it.

At junction of the destroyed and viable dermis—The capillaries of the normal dermis are not obviously profuse and are most prominent in the papillae

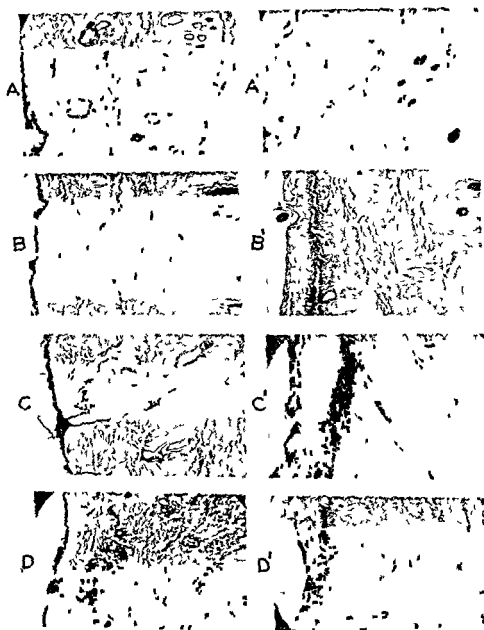


Fig. 1—16 (microphotographs) of the full thickness of epidermis and dermis of burn wounds from dogs at A twelve hours, B third day, C twenty-two hours, D fifty days without heparin, and A', B', C', D' at intervals during heparin therapy. (X150)

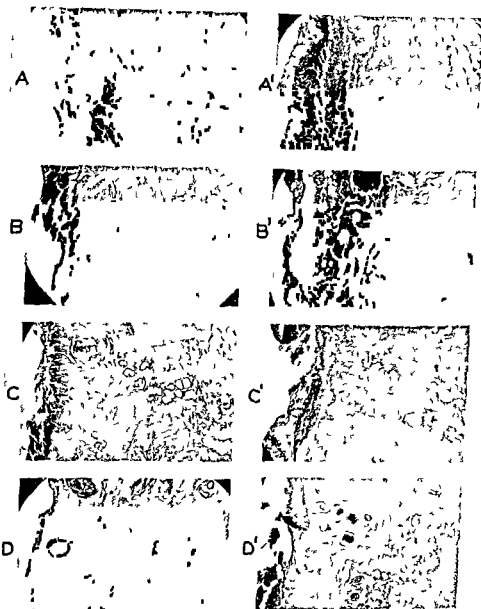


Fig. 1.—Photomicrographs of the epidermis and dermis of burns removed from Dog 10 at A nine days B eleven days C fifteen days D seventeen days. A D Same intervals during heparin therapy ($\times 45$)

of the dermis. Normally, following visible separation between the dying and viable dermis, there appears an increased number of capillaries which early, following a burn, seem to be old capillaries. By the thirty six hour period, these capillaries in the controls may be empty or packed with sludged abnormal red cells (Fig 3, A). In the heparinized animals by this same time, the sludging that was also seen in them initially, has largely disappeared and capillaries are seen containing normal red cells which seem to be in a normally circulating vascular network (Fig 3 A'). This same difference is still apparent in the seventy two hour burn (Fig 5 A and A') but is not common after this period. An auxiliary evidence of normal circulation in this layer is the appearance usually at thirty six hours of increased polymorphonuclear leucocytes in these capillaries of the heparinized animal. This occurs at seventy two hours or later in the majority of control animals. Increased numbers of capillaries at this zone appear at forty eight to seventy two hours quite prominently in the heparinized animals and is just beginning at three to five days in the controls.

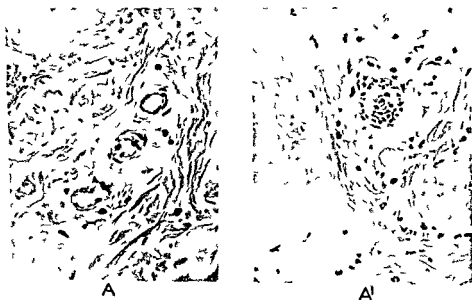


Fig 3.—Photomicrographs (Dog 6) Capillaries at junction between viable and nonviable dermis. A At thirty six hours without heparin A' with heparin (X400)

In the subcutaneous fat layer The large and small arteries in this zone tend to be normal throughout the entire experiment. At four and twelve hours following the burn there is some evidence that they are less full than normal. As time progresses they quickly return to normal filling and continue so from the forty-eight to seventy two hour period on in both groups (Figs 3 and 6). The large and small veins in this same area early are more full than normal and in both series of experimental animals show sludging and abnormal red blood cells present up to thirty six hours. Sludging first appears in both groups at the first examination, four hours following the burn. In general the sludging in the heparinized animals is largely gone by the thirty six hour examination and



Fig. 4.—Photomicrographs (Dog 5) of skin in subcutaneous fat layer subjacent to Fig. 3. A. At thirty-six hour without heparin. A'. With heparin. ($\times 400$)

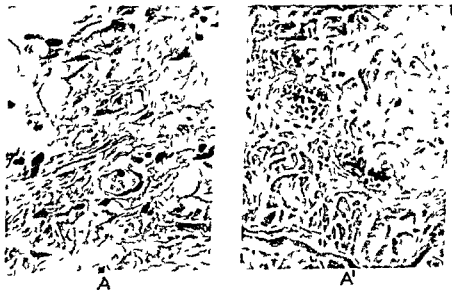


Fig. 5.—Same as Fig. 3 at sixty-two hours. ($\times 400$)

no further evidence of abnormal red cells is found (Fig 4, A and A') In the control animals this same change occurs at approximately seventy two hours (Fig 6) However increased distention and sludging in the veins are still seen in many of the control animals up until the fifth day As further evidence of normal circulation polymorphonuclear leucocytes begin to appear in the arteries and veins at approximately twelve hours in the heparinized series and not comparably in the controls until thirty six hours have passed By the fifth to seventh day all evidence of abnormal vascular arterial supply and venous return has disappeared in both experimental groups

In general therefore the heparinized animals give evidence of being twenty four to forty eight hours ahead of the control series during the first three days of the examination as pertains to functional blood supply



Fig 6—Same as Fig 4 at seventy two hours ($\times 400$)

In unburned tissue from the periphery In general sludging appears at the same time as mentioned in the subcutaneous fat tissue It disappears a little more slowly here in the controls but at the same time in the heparinized series as mentioned previously The appearance of polymorphonuclear leucocytes in these vessels very closely coincides with their arrival in the subcutaneous liver as does the disappearance of abnormal red cells

In the platysma muscle and subjacent to it The characteristic changes in the blood supply in the iris above are somewhat similar here However the sludging appears at a later time twelve hours in both heparinized and non heparinized animals but has disappeared by the thirty six hour period in the heparinized and by three to five days in the control animals The disappearance of abnormal red cells and the appearance of polymorphonuclear leucocytes closely coincides with the previous livers mentioned



Fig 4—Photomicrographs (Donor 3) of vein in subcutaneous fat layer subjacent to Fig 3
A At thirty-six hour without heparin A' With heparin (X400)

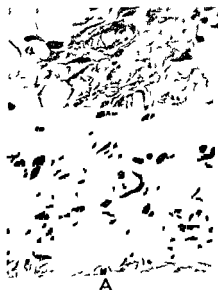


Fig 5—Same as Fig 3 at seventy-two hour (X400)

control animals at seventy two hours (Fig 10 A) During the third to seventh days following the burn infiltration here gradually recedes as that into the dermis reaches its maximum. This decrease is coincident with the beginning of capillary regeneration and fibroplasia in the layer where the subcutaneous fat is immediately subjacent to the dermis.

This mechanism of polymorphonuclear infiltration operate eventually to produce a marked separation of this sloughed tissue from the underlying granu-



Fig. 8—Same as Fig 7 and subjacent to it in the subcutaneous fat layer. ($\times 100$)



Fig. 9—Same as Fig 7 at seventy two hours. ($\times 100$)

One other vascular change of interest, in comparing the two series of animals is the capillary regeneration in the dermis and in the subcutaneous fat tissue. In the control animals active capillary regeneration in the dermis begins at approximately nine days and seems to reach a point around the ninth day that is first reached by the heparinized animal at five days (Figs 11, A', and 12, A). Capillary regeneration in the fat begins first in the heparinized animals at the third day (Fig 10, 1'), is marked by the fifth day (Fig 11, A'), and reaches a point at this time which is not usually reached before the ninth day in the controls (Fig 12, 1).



Fig 7—Photomicrographs (Fig 6) of polymorphonuclear infiltration in the dermis. A At thirty six hours without heparin. A' with heparin. (X100)

Infiltration of Polymorphonuclear Leucocytes—

Into the dermis and the junction of viable and nonviable dermis. Polymorphonuclear infiltration into the areas of the junction of viable and nonviable dermis in the heparinized animals is usually seen to begin around twenty four hours and is widespread by thirty six hours (Fig 7, 1') and generally reaches a comparable point in the control animals at seventy two hours (Fig 9 A). Fig 9 A and A', also shows the most common difference between the two groups of animals and demonstrates that by seventy two hours in the heparinized animal a well defined zone of demarcation has occurred between the viable and nonviable dermis. In general the maximum infiltration occurs by the ninth day in the heparinized animals (Fig 2, 1') and at eleven or fourteen days (Fig 2, B and C) in the controls.

Into the subcutaneous fat layer. In general the infiltration begins earlier in both series of animals in this layer than in the dermis. It is quite prominent by twelve hours in the heparinized series and by thirty six hours (Fig 8 A) has reached a point which is roughly comparable with that generally seen in the

control animals at seventy two hours (Fig 10, A). During the third to seventh days following the burn infiltration here gradually recedes as that into the dermis reaches its maximum. This decrease is coincident with the beginning of capillary regeneration and fibroplasia in the layer where the subcutaneous fat is immediately subjacent to the dermis.

This mechanism of polymorphonuclear infiltration operates eventually to produce a marked separation of this sloughed tissue from the underlying granu-



Fig 8—Same as Fig 7 and subjacent to it in the subcutaneous fat layer ($\times 100$)



Fig 9—Same as Fig 7 at seventy two hours ($\times 100$)

lation tissue. This seems to reach a maximum in the nine day heparinized series and in the fourteen day control series in general. It is not infrequently seen that a burn may reach the point of complete healing when it is still covered by slough (Figs 2 D' and 13 1).

Fibroplasia and Regeneration of Dermis—

In the hypodermis. The layer immediately subjacent to the dermis where it joins the subcutaneous fat tissue called the hypodermis by Moritz seems to

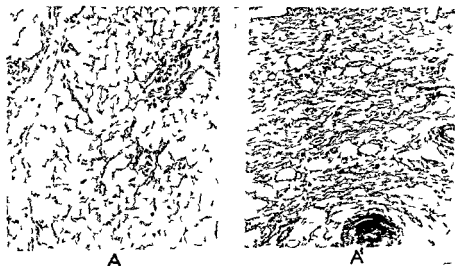


Fig. 10—Same as Fig. 8 at twenty-two hours (X100)

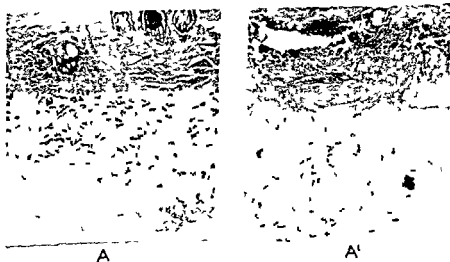


Fig. 11—Photomicrograph (Dog 10) of dermis and subcutaneous fat layer. Demonstrate fibroblasts and capillary regression in the fat and hypodermis and projection of fibroblastic curls toward surface. A At five days without heparin. A' With heparin. (X50)

be the most active source of young fibroblasts for the repair of the injured dermis. Early fibroblastic proliferation was seen at seventy two hours in this layer in all eight of the short term heparinized series and in only three of eight of the controls (Fig 10 A, A'). This is quite active by the fifth day in the heparinized series and reaches a point at that time which is roughly comparable to the nine day control animal (Figs 11 A', and 12 A). In both series this fibroplasia continued in two directions. First from the hypodermis fingerlike



A



A'

Fig 11—Same as Fig 10 at nine days (X20)



A



P

Fig 12—Histonecrops (Dog 10) at seventeen days. A Regenerated epithelium and young vascular fibroblastic tissue immediately beneath it (X10). P Dermis never destroyed by the injury demonstrating fibroplasia (X20).

projections of fibroblasts and young capillaries begin to work their way to the surface between the fascicles of normal dermal collagen. This is marked by the ninth day in the heparin group and reaches the surface in many places on the same day in most animals (Fig 12, A'). Second, the fibroblastic proliferation that occurs in the deeper layers of the subcutaneous fat tends to become adult in type, forming collagen similar to that of the normal dermis. This seems to reach a rather adult appearance by the eleventh day in the heparinized animals and earlier than in the controls (Fig 12, 1').

When projections of young fibroblasts finally reach the surface they seem to grow out on a base of old uninjured dermis and form a layer of young fibrous connective tissue. There is a large supply of young capillaries with it and it forms the final base on which epithelial regrowth occurs. This is seemingly true of all burns which initially destroy over 50 per cent of the dermis.

In the dermis. Another interesting phenomenon seems to occur at approximately the same time in both series of animals in the dermis that was never harmed by the initial burn. Around the eleventh day there seems to be a definite proliferation of the fibrocytes in the bundles of collagen. The cellularity of a unit of old dermis seems gradually but perceptibly to increase up to the end of the experiment at seventeen days (Fig 13). These fibroblasts seem to originate in situ and there appears to be no spatial connection between these and the cords of fibroblastic tissue coming to the surface from the hypodermis.

Final composition of the regenerated dermis. The two most obvious sources of the dermis finally underlying the regenerated epithelium are from the unburned collagenous connective tissue and from the young fibroblastic connective tissue that migrated from the proliferation in the hypodermis. This may be contributed to by the apparent fibroblastic proliferation that begins as mentioned previously in the fibrocytes of the undamaged dermis. In the severe burns destroying most of the collagen a good proportion of the final dermis is made up from the fibroblastic tissue that began in the subcutaneous fat connective tissue and the trabeculae of the old dermis. This gradually changes from its appearance in the heparinized animals on the fifth day (Fig 11, A') to that seen on the ninth day (Fig 12, 1') when the deepest portion of the dermis seems to be made from this maturing fibroblastic tissue in the area. From the eleventh day onward a variable portion of the dermis is made up of this source of connective tissue.

Dermal regeneration in burns destroying less than 30 to 40 per cent of the dermis. The foregoing statements regarding the sources of fibroblastic connective

ever seen any fibroblastic activity in the hypodermis as an adult connective tissue alongside the shafts of the hair follicle epithelium seems here to be the source of the fibroplasia. It forms the same sort of base for epithelial regeneration as previously described. The rich network of capillaries alongside these same hair follicle shafts seems to be the source of capillary regeneration which supplies this young connective tissue.

Epithelial Regeneration—Statements have been made which indicate that the final ability of the burned area to cover itself with new epithelium depends on the size of the burn and the depth of the burn. One of the difficulties encountered in controlling equality of burn in different animals was in the variable destruction of the hair follicle epithelium which normally goes deep into the dermis and the superficial layer of the subcutaneous fat. Some burns seeming to involve 60 to 70 per cent or more of the dermis did not destroy all of the potential epithelium at the base of the burn. Other burns involving only 50 per cent of the dermis destroyed every bit of potential epithelium. The median of the per cent of dermal destruction in the control series of burns was approximately 50 per cent while in the heparinized group the median was nearly 80 per cent.

It was however our definite impression from the study of the total microscopic material that the epithelial destruction with this deeper burn in the heparinized series was also most often accompanied by greater basal epithelial destruction. Consequently the determination of healing time does not seem to be a final criterion on which the two series may be separated. As a matter of fact approximately the same number of control and heparinized animals completely healed by the fourteenth day or by the seventeenth day. In some the controls healed more quickly and in others the heparinized animals. Because the final end result and time of complete healing depend primarily on initial total epithelial destruction we do not feel that this, therefore, indicates that heparin therapy was not producing definite benefits in the animals to which it was given. This will be discussed further in the paper.

In four of eight of the heparinized animals epithelial regeneration from the edges had definitely begun by the seventy two hour period, while it had not appeared in any of the control animals. The marginal regeneration by measurement of low power fields seemed most commonly to be approximately four days further advanced in the heparinized series. This seems to be a more accurate appraisal of the healing potentialities than total epithelial coverage. The same connective tissue proliferation mentioned as arising in the superficial dermis with more minor burns seems also to be the source of the initial fibroblastic scaffolding at the margins of severe burns.

Hughes and Dunn¹ have shown by injection of the blood supply to burned areas that the superficial vascular regeneration seems to come from the superficial layers of the dermis. It progresses from the margins toward the center of the burned area. Histologic evidence of this is easy to discern. Tonguelike projections of young epithelium grow out on this scaffolding from the periphery of the burn and are directed beneath the polymorphonuclear infiltrated layer. They rest on the young fibroblastic connective tissue whatever may have been its place of origin. Success or failure of these tentative and hopeful regenerative projections seems to depend entirely on the vascularity of this young connective tissue. Again here it is obvious that successful healing depends fundamentally on vascular supply.

thrombosis occurred in the vessels subjacent to a burn or that a complete loss of blood supply (anatomic) with secondary tissue necrosis resulted. The apparent sludging, which could result in a temporary loss of physiologic blood supply, seemed to recede much earlier in the heparinized series. This would explain the more effective response in this group.

Fig. 14 offers interesting information on this point. In six of eight animals in the three day control series, the excision wounds separated as shown in Fig. 14-1. This occurred in but one of eight of the heparinized group and was quite superficial in extent. Infection was not the cause of this phenomenon. It is explainable on the microscopic evidence that the same vascular congestion and sludging seen beneath the burn also extended into the unburned tissue at the periphery. The same width of excision and technique of closure were practiced in both groups. We believe this to offer further evidence of a better physiologic blood supply in the heparinized animals.

The animals chosen for photographic recording were those which most closely responded in a similar manner throughout the experiment. The differences in the two groups were most consistent when this fortuitous condition supervened and in these animals healing occurred at an appreciably earlier time in the heparin group. In other heparinized animals where the loss of dermis was greater than in the control phase it was most common that the entire basal epithelium was destroyed. Consequently the healing or regeneration of epithelium were used as the sole yardstick would be more slow than in the control animal with a less severe burn.

The most consistent differences in the heparinized phases of the experiment were in the earlier institution of (1) polymorphonuclear infiltration and separation of slough, (2) fibroblastic proliferation and vascular regeneration and (3) normal blood supply. The speed and effectiveness of tissue repair seem enhanced by heparin and in burns of strict comparability would lead to a shorter healing time in all such instances. It would seem from the foregoing data that the last ten of the seventeen days of heparin therapy in the experimental study might be unnecessary in a human therapeutic regimen. The same improved effectiveness of the blood supply and reparative mechanisms might be obtained by a short course of treatment for five to seven days at which time the blood supply seems normal even in the controls.

SUMMARY

1 Sixteen dogs were each given six one half inch square burns which were excised at intervals of from four hours to seventeen days. The same dogs were reburned and then heparinized throughout the experiment. Thus each served as its own control.

2 The normal reparative mechanisms are described and their proper function seems to be directly related to a normal blood supply.

3 Sludging and congestion of the subjacent venous channels occurred early in all animals, control and heparinized, but thrombosis was not a common occurrence in either.

DISCUSSION AND CONCLUSIONS

The analysis of our experimental data seems to indicate that the addition of heparin therapy to the treatment of a burn definitely speeds up the processes of normal tissue repair. In general we found that the heparinized animals reached a comparable point at thirty six hours that the control animals reached in three days. Similarly, at five days the heparinized burns showed an equivalent amount of reparative activity most commonly seen in our nine day control animals. This approximate difference of four days is also apparent at the seven and eleventh day periods of the two series. No further progression in the amount of difference between the two series seemed to occur after this time. This correlates with the fact that in most all of the controls the blood supply had apparently returned to normal by the fifth to the seventh day.



Fig. 14.—A Without heparin. Granulating scar tissue resulting from separation of sutured excision wounds after a three day experiment. At this time they are from thirty to sixteen days old. A' With heparin on the opposite side of the same dog. The wounds are six to nine days old.

If this impression be true then it is necessary to explain the fact that the control and heparinized animals often healed at a comparable time. Unfortunately it is extremely difficult using the same animal for his own control and the same technique of burning to produce identical burn each time. It also occurred that the median loss of dermis in the control group was approximately 50 per cent versus 80 per cent in the heparinized group. This greater loss of dermis in the heparinized series was not due to the heparin therapy. Burns removed from both groups near the end of the experiment frequently showed less dermis loss than specimens removed at five nine eleven days etc. It was due apparently to slight changes in the accuracy of the muffle furnace used to heat the steel blocks in the first part of the experiment. Even the use of boiling water as a method of heating the blocks did not completely eradicate this difference in the response of the same animal to the same amount of heat.

Unquestionably the amount of undestroyed epithelium is the major factor determining time of complete healing. The only possible value of heparin seems to be not in adding a new mechanism of healing but in enhancing general tissue repair in the point of view of time. We found no evidence to suggest that

Review of Recent Meetings

MEETING OF THE SOCIETY OF UNIVERSITY SURGEONS

HARRIS B. SHUMACKER, JR. M.D. INDIANAPOLIS, IND.

THE tenth annual meeting of the Society of University Surgeons was held in San Francisco, Calif. March 24, 25 and 26, 1949. Hosts to the Society were the departments of surgery of the University of California School of Medicine and the Stanford University School of Medicine.

On the first morning of the meeting, after welcoming remarks by Dr. Loren R. Chandler, the following papers were presented by members of the Stanford University School of Medicine:

- Clinical and Pathological Studies of Fat Neurosis—Nelson J. Howard
- The Splint Suture of Blood Vessels—Edgar J. Poth
- Experiences With Carotid Cavernous Fistula—Frank Gerbode, Emile Holman and Victor Richards
- The Relationship of Portal Hypertension and the Irreversibility of Shock—Poy B. Cohn and Harry G. Parsons
- Preliminary Report on Experimental Ascites—Harry G. Parsons and Emile Holman
- Approach to the Problem of Stimulating Bone Growth—Victor Richards
- Experimental Intramedullary Nailing: The Occurrence of Fat Embolism—August W. Meier
- Internal Drainage of Pancreatic Pseudocysts—Carleton Mathewson, Jr.
- Experimental Atriacaval Shunts—James Lee and Frank Gerbode
- Late Treatment Problems of the Burned Hand—L. D. Howard
- Surgical Treatment of Adhesive Pericarditis—Emile Holman

On the afternoon of the first day of the meeting, after welcoming remarks by Dr. Francis Smyth, the following papers were presented by members of the University of California School of Medicine:

Mr. A. - C.

- to Anesthesia—John B. de C. M. Saunders
- Regeneration of Thyroid Tissue Following Subtotal Thyroidectomy—Horace J. McCorkle
- Clinical and Pathological Studies of Benign and Malignant Gastric Ulcer—Orville Grimes
- Intravenous Amino Acid Tolerance Studies in Humans—Harold A. Harper
- Local Heparinization in Conjunction With Arterial Embolectomy—Edwin J. Wyhe
- Report of an Unusual Case of Huge Cystic Adrenal Tumor—H. Glenn Bell
- The External Use of Radioactive Iodophorus in the Treatment of Benign and Malignant Epithelial Growths—P. V. A. Low Beer
- Cholelithogastrostomy by Means of Gastric Mucosal Tube for the Repair of Certain Strictures of the Bile Ducts—Leon Goldman

4 The blood supply subjacent to a burn returns to normal by the fifth to seventh days in the control group and by thirty six to seventy two hours in the heparin group

5 This fundamental difference seems to produce a marked enhancement of the speed and effectiveness of the repair mechanisms in the heparinized animals. On the fifth day the heparin group is generally at a similar point reached on the ninth day by the controls

6 A study of the data indicates that a five to seven day course of heparin therapy would produce the same benefits as observed in the seventeen day experimental regimen

REFERENCES

- 1 Hughes A F W and Dunn L Vascular Regeneration in Experimental Wounds and Burns Brit J Exper Path 22 9 1941
 - 2 Leach F H Peters R A. and Rossiter R J Experimental Thermal Burns Especially the Moderate Temperature Burn Quart J Exper Physiol 32 67 1943
 - 3 Moritz A R, and Henriques F C Jr Studies of Thermal Injury II The Relative Importance of Time and Surface Temperature in the Causation of Cutaneous Burns Am J Path 23 69, 1947
 - 4 Moritz A R Studies of Thermal Injury III The Pathology and Pathogenesis of
- 5 I
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- Water

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Original Communications

THE TREATMENT OF ADVANCED MAMMARY CANCER WITH ESTROGENS

MAR CUTLER MD, MELVIN SCHLEMPSON MD,* AND JOHN J KLEINER, MD
CHICAGO ILL, AND EDUARDO CACERES MD, LIMA, PERU

(From the Chicago Tumor Institute)

THE purpose of this paper is to record the results in 20 consecutive cases of advanced cancer of the breast treated with estrogens

Since its isolation in 1923 the growth stimulating properties of the follicular hormone have been well established and generally accepted.^{1,2,3} In 1942 a group of English investigators demonstrated the growth inhibiting effects of estrogens in laboratory animals.⁴ This led to the use of estrogens in human beings with advanced mammary cancer. Haddow and his group⁵ in 1944 reported palliative results in 10 of 22 cases of advanced breast cancer treated with triphenyl chloroethylene and in 5 of 14 cases treated with stilbestrol. The favorable effects were confined almost exclusively to the older age group. In addition Koller⁶ (a member of Haddow's group) described microscopic changes which occurred during estrogen therapy. In the same year several groups of English investigators presented 169 cases of advanced breast cancer treated with stilbestrol with the results shown in Table I.

Nathanson⁷ has treated over 150 cases with various estrogens at the Massachusetts General Hospital. The results in isolated cases have been published^{8,9,10} but no detailed report has as yet appeared. Herrman, Adair, and Woodward¹ treated 17 cases with ethinyl estradiol and noted favorable responses in 7.

CASE REPORTS

Twenty patients were treated. Thirteen were not benefited and the disease progressed; metastases to bone were present in 4 of these 13 and in 1 of the other 7. 1 patient demonstrated improvement in a bone lesion. In 7 cases there was definite improvement; in 3 the disease was temporarily arrested and a marked improvement in the general condition was observed; in 4 ulcers of the breast healed and in 1 of these metastasis to a lumbar vertebra showed deposition of calcium.

Large doses of both synthetic and natural estrogenic substances were used: diethylstilbestrol monomethyl ether (Monomestrol), stilbestrol (oral and intramuscular) and a solution of estrogens in oil principally estrone (intramuscular).

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On the following days of the meeting papers were presented by members of the Society. In addition to those which are published in this issue of the JOURNAL, the following papers were presented or read by title:

- Tumors of the Parotid Gland—Polert W. Puxton
 Measurements of Healing, Strength of a Standard Wound in Anemia or Starvation Status and After Treatment With Blood Transfusions or Refeeding—Richard L. Varco, Yoshio Soko, and Arnold Kremen
 Intrahepatic Cholangiojejunostomy With Partial Hepatectomy—A Useful Addition to Technical Methods for the Management of Common Duct Stricture—Harwell Wilton
 Simple Excision of Lung Abscess—Cranston W. Holman
 The Radical Treatment of Lymphangioma of the Shoulder and Hip in Infants and Children—Mark M. Ravitch
 Complications Following Ichoectomy and Pneumonecstomy for Tuberculosis—Rollin A. Daniel, Jr., and Douglas H. Pritchell
 The Role of Tracheotomy in the Postoperative Treatment of Esophagectomized Patients—John T. Reynolds, Paul H. Holinger, Albert H. Andrews, Jr., John P. Young, Jr., and William H. Marlowe

The presidential address by John S. Lockwood presented at the annual dinner was concerned with future plans of the Society.

heal rapidly. She then developed signs of cardiac decompensation and was treated with digitalis. On June 6, 1948, there was complete healing of the ulcer and regression of the underlying mass, the patient then became irregular in reporting for treatment and on July 9, 1948, the lesion had again ulcerated and the disease was progressing. After the patient was persuaded to resume regular treatment, the ulcer again healed and on Aug. 3, 1948, the disease appeared stationary. The patient has received 140 mg. of estradiol dipropionate and treatment is continuing.

Fig. 1



Fig. 2.

Fig. 1 (Case 2)—Before treatment.
Fig. 2 (Case 2)—After treatment.

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Fig. 1



Fig. 2

Fig. 1 (Case *)—Before treatment.
Fig. 2 (Case *)—After treatment.

Comment—The duplication of the initial response to estrogen therapy demonstrates that the healing of an ulcer is not the end point in a reaction and that regular treatment is indicated thereafter until recrudescence of the disease takes place and should be continued until it is established whether further and is or is not to be obtained

CASE 4—A woman, aged 75 year, was admitted on May 14, 1948. In 1943, a cancer of the left breast had been treated with removable radium needles with complete regression of the mass. In February, 1948, an ulcerated mass appeared in the treated



A B
Fig 3 (Case 4)—Before treatment.



A B
Fig 4 (Case 4)—After treatment.

area. On admission May 14 1948, there was an area of ulceration 8 by 8 cm in the upper, outer quadrant of the left breast and a hard mass in the left axilla. In addition there was a mass in the right breast characteristic of cancer and a hard node in the right axilla and left suprascapular area. There was no metastasis in the lungs. An osteolytic area was seen in the fourth lumbar vertebra (Fig 3, A and P). Biopsy examination of the ulcerated area disclosed carcinoma. The patient received 15 mg of stilbestrol orally daily. The ulcerated area showed progressive healing and the general condition of the patient improved. On Aug 9 1948 there was regression of the metastatic nodes and almost complete healing of the ulcerated area. Deposition of calcium in the bone metastasis was manifest (Fig 4, A and B). The patient has received 1120 mg of stilbestrol and treatment is continuing.

Comment—This case illustrates the healing of a carcinomatous ulcer and the concomitant improvement in a bone metastasis.

DISCUSSION

The physiologic effects of estrogen are well known. Patients under treatment with large doses occasionally develop other manifestations including deep pigmentation of the areola, uterine bleeding (during or following treatment), softening of the skin and generalized edema. This latter effect probably results from disturbance of the electrolyte balance.¹⁴ Toxic effects such as nausea, vomiting, and abdominal cramps occur occasionally, but usually are controlled by interrupting the medication or by changing to another estrogen. However, we have seen several patients who were unable to tolerate large doses of estrogens in any form.

The general scheme of response follows a pattern similar to that reported in the English study.⁷ It appears that palliation can be expected most frequently in patients over 60 years of age and in a relatively small number of patients under 60 years. The relationship of response to age is tabulated in Table II.

TABLE II

AGE (YR.)	IMPROVED	NOT IMPROVED	TOTAL
Over 60	3	3	6
Under 60	2	10	12
Total	5	13	18

The exact duration of palliation in our cases cannot be discussed at this time as the patients have not been observed long enough. It is our impression that

cases which respond favorably. In this way the duration of response will be determined. More precise information will be forthcoming from a study being conducted by the Therapeutic Trials Committee of the American M. A.

It has been suggested that metastasis may occur in young women¹⁵ and estrogen must be used cautiously in that group.

SUMMARY AND CONCLUSIONS

1. Twenty consecutive cases of advanced cancer of the breast were treated with estrogenic substances. Palliative effects were observed in seven.

- 2 The palliation occurred most frequently in the patients over 60 years of age
- 3 The effect was evident in both bone and soft tissue metastases
- 4 Several estrogenic substances were used, but no difference in response was noted. The optimal doses have not been established
- 5 Vaginal bleeding occurred in some patients
- 6 The duration of palliation has not as yet been determined
- 7 It is our impression that certain patients with advanced cancer of the breast experience relief from pain and a sense of well being during estrogen therapy, even in the absence of objective improvement
- 8 No evidence that estrogens can cure cancer of the breast was found

REFERENCES

- 1 Allen Edgar, and Doisy, E. A. An Ovarian Hormone. A Preliminary Report J A M A 81 819, 1923
- 2 Allen Edgar, and Doisy, E. A. The Ovarian Hormone. J Biol Chem 61 1, 1924
- 3 Allen Edgar, and Doisy, E. A. The Ovarian Hormone. J Biol Chem 61 1, 1924
- 4 Allen Edgar, and Doisy, E. A. The Ovarian Hormone. J Biol Chem 61 1, 1924
- 5 Allen Edgar, and Doisy, E. A. The Ovarian Hormone. J Biol Chem 61 1, 1924
- 6 Allen Edgar, and Doisy, E. A. The Ovarian Hormone. J Biol Chem 61 1, 1924
- 7 Allen Edgar, and Doisy, E. A. The Ovarian Hormone. J Biol Chem 61 1, 1924
- 8 Allen Edgar, and Doisy, E. A. The Ovarian Hormone. J Biol Chem 61 1, 1924
- 9 Allen Edgar, and Doisy, E. A. The Ovarian Hormone. J Biol Chem 61 1, 1924
- 10 Nathan on I. Hormonal Alteration of Advanced Cancer of the Breast S Clin North America 27 1144 1947
- 11 Nathan on I. Influence of Stilbestrol on Advanced Cancer of the Breast J Clin Investigation 25 930 1946
- 12 Herrman J B Adair F E and Woodard H Q. Effect of Estrogenic Hormones on Advanced Carcinoma of the Female Breast Arch Surg 54 1 1947
- 13 Allen W M. The Biological Activity of Various Estrogens South W J 37 210, 1944.
- 14 Thorn G W and Engel L L. The Effect of Sex Hormones on the Renal Excretion of Electrolytes J Exper Med 68 209 1935

A MAMMAPLASTIC SUBSTITUTE FOR AMPUTATION IN HYPERTROPHIES

JACQUES W. MALINTAC, M.D., NEW YORK, N. Y.

GENERAL CONSIDERATIONS

THE following modification of the classical retromammary procedures has proved a satisfactory substitute for mastectomy with free grafting of the nipple in several types of massive hypertrophy. It is particularly indicated when reduction of the anteroposterior diameter of the breast is the chief objective and retention of sensitivity in the nipple is an important consideration.¹ It cannot be employed when the areola is greatly enlarged.

The retromammary approach was first described by Thomas and Warren² for the removal of benign tumors. Subsequently Guinard³ and Morestin⁴ followed this route for plastic excision in breast hypertrophies. Apparently none of these authors recognized the necessity for plastic reconstruction of the skin covering to impart proper form, and adequate mastopexy to ensure permanence of results.

The great advantage of the submammary route lies in its safety. It permits wide exposure of the posterior aspect of the breast and extensive glandular resection without jeopardy to the main mammary blood supply and its periareolar ramifications⁵ (Fig. 1). It also facilitates fixation of the breast to the pectoral muscle.

Because of its safety factor this procedure can often be carried out in one stage. However two stages are preferable allowing greater attention to fine detail in the pursuit of an optimum end result.

PROCEDURE

Glandular Resections—An incision is made in the submammary fold through which the posterior surface of the breast is bluntly separated along the retromammary aponeurosis as far as the second intercostal space. The breast is then turned over on the chest and its posterior aspect exposed for glandular resection. The type of excision varies with the nature and degree of the hypertrophy (Fig. 2).

Reduction of the gland is effected in such manner as to preserve the bulk of its central portion. Excisions are made in the external and lower quadrants where enlargement is usually greatest. As a rule bleeding is minimal because of the disposition of the blood supply; the surgical area can be shaped without danger of interference with the main vascularization of the nipple.

In enlargements associated with isolated benign tumors (cysts, fibroadenomas, etc.) a number of V-shaped segments can be taken from the entire thickness of the gland, each including one or more growths. No attempt is made to decapsulate cysts as they are usually adherent to the surrounding tissue and may open during the process of separation. If the breast appears

undesirably flat the radial sections of the gland should be overlapped before suturing to produce conical protrusion

Mastopexy—*Firm affixation of the reconstructed breast* is an essential element in this as in all mammaplastic procedures. The distended atrophied skin cannot be relied upon to maintain the organ in position even when a proper skin plastic is done. Absorbable sutures are also unreliable. To counteract the natural tendency of the breast to descend resilient nonabsorbable suture material should be used.

The discarded excised skin affords an ideal substance for this purpose. A strip of suitable size is placed under traction and the epithelium shaved off with a skin graft knife. Three or four strips eight to ten inches long and one third inch wide, usually suffice for firm affixation (Fig 3). No other nonabsorbable material offers as great assurance of permanence and as little risk in the poorly vascularized, friable tissue of this area.

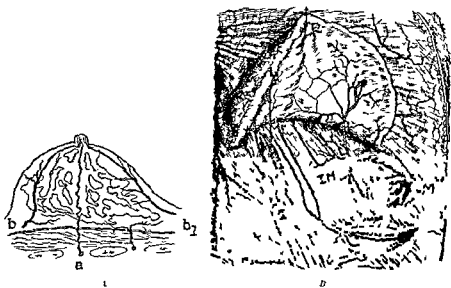


Fig 1—Blood supply posterior aspect of breast. A Sagittal horizontal section showing main perfusing vessels and their branches (b, b1, b2) in subcutaneous structure at levels varying from 0.5 to 5 cm according to amount of fat. These must be retained (a). The relatively unimportant intercostal penetrating glands from behind and playing an essential role in supplying the nipple. The vertical section of nipple shown here is rare. B Main retromammary arteries (IM) originating from internal mammary artery (IM). The less important intercostals (I) derive from aorta. These long vessels are easily separated in retromammary resection (Gillman).

The dermal loops are inserted vertically through gland and pectoral muscle with a long fascia needle catgut sutures secure the knots in place. The loops are placed to the side of the midline so as to cause the middle segment of the breast to protrude in cone shape.

Skin Plastic—Following reduction and affixation of the gland the skin covering must be adjusted to conform to the reduced breast (Fig 4). One of the chief disadvantages of a retromammary procedure is the flatness resulting from failure to do this. Wide lateral undermining of the flaps accompanied

by adequate excision in both vertical and horizontal diameters, is required for even distribution of the skin. Ample fatty padding of the lateral flaps should be retained beyond the areolar zone.

When protuberance of the breast is the chief problem retromammary resection may suffice for repair without a skin plastic.

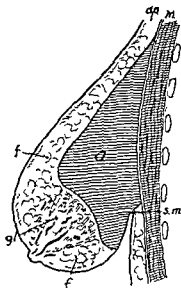


Fig. 2

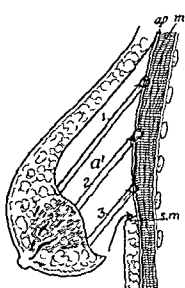
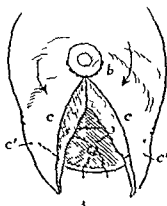


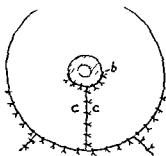
Fig. 3

Fig. 2—Area of retromammary excision (a) varying according to case but preserving central core of gland (pl) and subcutaneous blood vessels and fat. Posterior surface of breast partly separated along pectoral aponeurosis (ap) through incision in submammary fold (sm). (f) Skin flaps. (m) pectoral muscle.

Fig. 3—Incision of diamond loop (1, 2) through posterior aspect of reduced breast and pectoral muscle (m). (a) Retromammary piece following excision. (b) Submammary fold (ap) shown in situ.



A



B

Fig. 4—Skin flaps (a) following incision along lower border of areola (b) midline and submammary fold (c) are mobilized. Excisions along midline and submammary fold (c').

B After closure of flaps under areola (b) and along midline (c) and submammary fold (c').

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Mastopexy—Firm affixation of the reconstructed breast is an essential element in this as in all mammoplasty procedures. The distended atrophied skin cannot be relied upon to maintain the organ in position even when a proper skin plastic is done. Absorbable sutures are also unreliable. To counteract the natural tendency of the breast to descend, resilient nonabsorbable suture material should be used.

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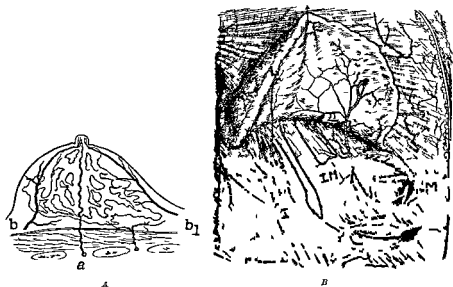


Fig 1—Blood supply posterior aspect of breast. The main perforating vessels and their branches vary from 0.5 to 2.5 cm according to area. The intercostal arteries penetrate the breast to supply the nipple. (The direct penetration of the main retro-mammary arteries (IM) is an important intercostal artery (I) derived from the retro-mammary vessels (Salmon).)

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THE IMPLICATIONS OF LOCAL EXCISION OR SIMPLE MASTECTOMY PRIOR TO RADICAL MASTECTOMY FOR CARCINOMA OF THE BREAST

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Department of Surgical Pathology, Washington University School of Medicine and
Farnes Hospital, St. Louis, Mo.)*

A STUDY was made of 41 patients with proved carcinoma of the breast who had had simple mastectomy or local excision of the tumor prior to entering the Ellis Fischel State Cancer Hospital. The undesirable results which follow the use of simple mastectomy performed for diagnostic purposes or for any other reason prior to radical mastectomy are emphasized. The cases presented suggest that local excision followed by a delay of over two months may be detrimental to the ultimate welfare of the patient.

It has been the experience of others that poor surgical results are obtained from secondary radical operation after primary surgical excision or simple mastectomy in carcinoma of the breast. Adair¹ stated: "Of 283 cases classified as 'operable after local excision' there was a salvage of only 53 cases representing 20 per cent. Had the patient been properly handled at the beginning she at least would have had a 51 per cent chance of a 5 year cure." Harrington² reported in 1940 that 10 per cent of the patients with radical mastectomies done at the Mayo Clinic had had previous minor surgical procedures done elsewhere and that 74 per cent of this group had lymphatic involvement as compared with 63 per cent who had not had a previous operation.

Greenough³ was of the opinion that exploration followed shortly by radical mastectomy diminishes little if at all a good prognosis in early carcinoma of the breast. He advised however that "delay between exploration and radical operation in cancer of the breast is to be avoided and that exploration should not be done unless and until all arrangements for competent pathological examination by frozen section and immediate radical operation are available. In a series of 42 early cases with exploratory incisions there were 33 per cent five year cures. Siemens⁴ in comparing 59 cases in which biopsies were done with 260 cases with no biopsies reported even better results in this group of 59 but emphasized that the good results were due to the fact that the lesions were noted earlier than in the 260 with no biopsies; that the tumor area was small and the axillary metastases were limited. He showed that a better survival rate was maintained in these cases in spite of biopsy and felt that biopsy in itself did not produce an untoward effect on the prognosis. Discussing these 59 cases in which biopsy was done at varying intervals prior to operation Siemens indicated that the prognosis was

The method described herein is not suitable when a greatly oversized areola requires circular excision. In such cases mammectomy or the two stage procedure of transposition¹ is indicated. However, a moderately wide areola can be safely reduced with this technique by excision along its lower border. Dissection in the areolar region must necessarily be superficial to preserve the periareolar venous and arterial plexuses.

SUMMARY AND CONCLUSIONS

1 The retromammary procedure described here affords a substitute for mammectomy with free grafting of the nipple (1) when the hypertrophy is mainly in the anteroposterior diameter and (2) when it is desired to preserve the sensitivity of the nipple. A greatly oversized areola is a contraindication.

2 The procedure consists of retromammary resections from the gland, the central segment including the nipple is preserved. This is followed by mastopexy by means of dermal loops and a double flap skin plastic.

3 This method preserves the sensitivity of the nipple, which is lost or greatly reduced after mammectomy with free transplantation of the nipple.

4 Because of the absence of any interference with the main mammary vessels the procedure can often be carried out safely in one stage.

REFERENCES

- 1 Maliniac J W. Amputation Versus Transposition of Gland and Nipple in Mammary Hypertrophy. *Annals of Plastic and Reconstructive Surgery* 1: 329, 1943.
- 2 Maliniac J W. Amputation Versus Transposition of Gland and Nipple in Mammary Hypertrophy. *Annals of Plastic and Reconstructive Surgery* 1: 329, 1943.
- 3 Maliniac J W. Amputation Versus Transposition of Gland and Nipple in Mammary Hypertrophy. *Annals of Plastic and Reconstructive Surgery* 1: 329, 1943.
- 4 Maliniac J W. Amputation Versus Transposition of Gland and Nipple in Mammary Hypertrophy. *Annals of Plastic and Reconstructive Surgery* 1: 329, 1943.
- 5 Maliniac J W. Amputation Versus Transposition of Gland and Nipple in Mammary Hypertrophy. *Annals of Plastic and Reconstructive Surgery* 1: 329, 1943.
- 6 Maliniac J W. Amputation Versus Transposition of Gland and Nipple in Mammary Hypertrophy. *Annals of Plastic and Reconstructive Surgery* 1: 329, 1943.
- 7 Maliniac J W. Amputation Versus Transposition of Gland and Nipple in Mammary Hypertrophy. *Annals of Plastic and Reconstructive Surgery* 1: 329, 1943.
- 8 Maliniac J W. Amputation Versus Transposition of Gland and Nipple in Mammary Hypertrophy. *Annals of Plastic and Reconstructive Surgery* 1: 329, 1943.
- 9 Maliniac J W. Amputation Versus Transposition of Gland and Nipple in Mammary Hypertrophy. *Annals of Plastic and Reconstructive Surgery* 1: 329, 1943.
- 10 Maliniac J W. Amputation Versus Transposition of Gland and Nipple in Mammary Hypertrophy. *Annals of Plastic and Reconstructive Surgery* 1: 329, 1943.

TABLE II NINETEEN PATIENTS CONSIDERED INOPERABLE ON ADMISSION, TIME INTERVAL FROM FIRST TREATMENT TO ADMISSION TO ELLIS FISCHER STATE CANCER HOSPITAL

INTERVAL	NUMBER OF CASES
1 to 2 months	5
7 to 9 months	3
11 months	1
20 to 60 months	7
1. to 21 years	3

All of these patients are now dead

In the 19 patients in whom radical mastectomy was not done, the intervals of time from initial treatment to admission to our hospital were relatively longer only 5 being admitted within two months following primary surgery.

Of the 12 patients who received radical mastectomy but are no longer living 4 died within three to five months and another 4 before twenty two months had passed. In view of the fact that the patients not receiving subsequent radical mastectomy survived relatively greater lengths of time from initial treatment to death we wonder if the patients' lives were not actually shortened by the second operation. Twelve of the 19 patients who were not given radical operation lived longer than thirty months. Six patients lived from eleven to twenty one months and only one died within a short period (two months). Of 11 patients receiving secondary radical mastectomy and subsequently dying from cancer tumor was present in all of the operative specimens in either the breast (1 case) axillary nodes (4 cases) or both (6 cases). The twelfth death was caused by a pulmonary embolus.

In the 22 patients who had radical mastectomy there was considerable inaccuracy in the clinical examinations with regard to the presence of persistent tumor or axillary involvement. Errors (proved by pathologic examination of the specimen) were made in 12 (or 55 per cent) of the 22 cases these mistakes usually made from not detecting the presence of actual axillary involvement. Other authors have quoted as high as 50 per cent error in this regard (Hargensen).

In 13 patients who had simple mastectomies prior to referral to our hospital the radical operation was not carried out because they were considered inoperable upon arrival (see Table III). All of these patients have since died 8 within one year of admission. Seven were given radiotherapy as a palliative measure but life was not noticeably lengthened in these instances. It is interesting to observe the high incidence of local recurrences in this group as well as the presence of regional lymphatic involvement and distant metastases. Every case with one exception revealed evidence of at least one of these three phases of the disease and several cases exhibited all three.

In only 6 patients with previous simple mastectomies was it feasible to do radical mastectomy and only 2 of these are now living without disease. Three died in relatively short periods following operation (2 lived two months and 1 lived thirteen months). In the 2 living patients there was no evidence of axillary spread or persistent carcinoma in the surgical specimen evidently demonstrating that the tumor was initially so small it was completely excised at the time of simple mastectomy. In the remaining 4 patients all had evi-

slightly worse when the interval between biopsy and operation was forty five days or more is compared to delays of from one to 10 days

It is generally conceded that biopsy of breast tumors in itself is not a dangerous procedure unless undue delay takes place between biopsy and subsequent radical operation. When a patient has a simple lump in the breast the tumor should be exposed in the operating room and if there is any doubt as to the nature of the tissue a frozen section should be done. Hargensen⁷ has indicated that the procedure which least disturbs the tumor bed and which theoretically is the best is the incisional biopsy. This is especially true in the larger more extensive tumors. It seems justified however when the suspicious single nodule is small (2 or 3 cm.) to remove it en bloc with a margin of healthy surrounding breast tissue. This gives the pathologist an opportunity to cut the entire nodule and do frozen sections as indicated. We have had several nodules in which carcinoma was present in only a small area which could easily have been missed by an incisional biopsy. With larger lesions excision en bloc is of course not practicable for frozen section incisional biopsy should be performed when there is any doubt as to the nature of the process. The sharp scalpel rather than the cautery is recommended.

Simple mastectomy should not be used as a diagnostic procedure under any circumstances. Slaughter and Peterson⁸ reported 13 patients who had had simple mastectomies for proved cancer and all but 2 presented local recurrences when they were examined for the first time in the tumor clinic. Hicken⁹ has shown that complete excision of mammary tissues is seldom accomplished in the usual simple mastectomy and that if the tumor is at all extensive carcinoma is very likely to be left in the remaining breast parenchyma. Aspiration biopsy should also not be used as a diagnostic method in breast carcinoma (Hargensen⁷) for in this procedure the malignant area may be missed or the material may be insufficient to distinguish architectural details and consequently unsatisfactory for accurate diagnosis.

Of the 41 cases in our group 22 patients had radical mastectomies in our hospital (16 of these had had previous local excisions of the tumor and 6 had had previous simple mastectomies) and the remaining 19 patients were considered to be inoperable on admission and were given either palliative irradiation or no treatment at all. Of these 19 patients 6 had had previous local excision and 13 had had previous simple mastectomy. Of the entire group of 41 cases only 9 patients are living without disease and these had time intervals of two months or less between the primary procedure and radical mastectomy.

TABLE I TWENTY TWO PATIENTS UNDERGOING RADICAL MASTECTOMY TIME INTERVAL FROM FIRST TO SECOND TREATMENT

INTERVAL	NUMBER OF CASES
1 to - months	14 (all of the 9 patients living, and 1 well were in this group)
3 to 4 months	3
5 to 10 months	2
24 to 48 month	3

TABLE II NINETEEN PATIENTS CONSIDERED INOPERABLE ON ADMISSION TIME INTERVAL FROM FIRST TREATMENT TO ADMISSION TO ELLIS FISCHER STADT CANCER HOSPITAL

INTERVAL	NUMBER OF CASES
1 to 2 months	2
7 to 9 months	3
11 months	1
20 to 60 months	7
1- to 21 years	3

All of the 19 patients are now dead

In the 19 patients in whom radical mastectomy was not done, the intervals of time from initial treatment to admission to our hospital were relatively longer, only 5 being admitted within two months following primary surgery.

Of the 12 patients who received radical mastectomy but are no longer living 4 died within three to five months and another 4 before twenty two months had passed. In view of the fact that the patients not receiving subsequent radical mastectomy survived relatively greater lengths of time from initial treatment to death we wonder if the patients' lives were not actually shortened by the second operation. Twelve of the 19 patients who were not given radical operation lived longer than thirty months. Six patients lived from eleven to twenty one months and only one died within a short period (two months). Of 11 patients receiving secondary radical mastectomy and subsequently dying from cancer tumor was present in all of the operative specimens in either the breast (1 case), axillary nodes (4 cases), or both (6 cases). The twelfth death was caused by a pulmonary embolus.

In the 22 patients who had radical mastectomy, there was considerable inaccuracy in the clinical examinations with regard to the presence of persistent tumor or axillary involvement. Errors (proved by pathologic examination of the specimen) were made in 12 (or 55 per cent) of the 22 cases. These mistakes usually made from not detecting the presence of residual axillary involvement. Other authors have quoted as high as 50 per cent error in this regard (Hjorgensen).

In 13 patients who had simple mastectomies prior to referral to our hospital, the radical operation was not carried out because they were considered inoperable upon arrival (see Table III). All of these patients have since died 8 within one year of admission. Seven were given radiotherapy as a palliative measure but life was not noticeably lengthened in these instances. It is interesting to observe the high incidence of local recurrences in this group as well as the presence of regional lymphatic involvement and distant metastases. Every case with one exception revealed evidence of at least one of these three phases of the disease and several cases exhibited all three.

In only 6 patients with previous simple mastectomies was it feasible to do radical mastectomy and only 2 of these are now living without disease. Three died in relatively short periods following operation (2 lived two months and 1 lived thirteen months). In the 2 living patients there was no evidence of axillary spread or persistent carcinoma in the surgical specimen, evidently demonstrating that the tumor was initially so small it was completely excised at the time of simple mastectomy. In the remaining 4 patients all had evi-

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Of the 41 cases in our group 22 patients had radical mastectomies in our hospital (16 of these had had previous local excisions of the tumor, and 6 had had previous simple mastectomies) and the remaining 19 patients were considered to be inoperable on admission and were given either palliative or radiation or no treatment at all. Of these 19 patients 6 had had previous local excision and 13 had had previous simple mastectomy. Of the entire group of 41 cases only 9 patients are living without disease and these had time intervals of two months or less between the primary procedure and radical mastectomy.

TABLE I. TWENTY TWO PATIENTS RECEIVING RADICAL MASTECTOMY. TIME INTERVAL FROM FIRST TO SECOND TREATMENT

INTERVAL	NUMBER OF CASES
1 to 2 months	14 (all of the 9 patients living and well were in this group)
3 to 4 months	3
5 to 10 months	2
24 to 48 months	4

dence of axillary involvement and 3 of these had local recurrences (with muscle invasion, etc.) as well. The final results in this group were notably poor even though the interval of time between simple and radical mastectomy was not unduly long. 1 with intervals of two months or less and 2 with intervals of four and seven months respectively. Fig 1 the photomicrograph illustrates the typical picture of local recurrence following simple mastectomy.

The 9 patients who are living without evidence of disease all had intervals of two months or less. This emphasizes the importance of the short interval between initial biopsy and radical treatment. The prognosis was uniformly good in spite of the fact that 3 of these patients had persistent tumor in the pathologic specimen at the site of previous excision. It is significant that the size of the removed tumors was uniformly small. Seven of these patients were previously treated by local excision while the other 2 had previous simple mastectomies (see Table III).

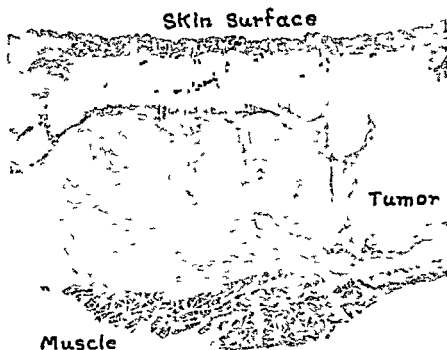


Fig 1—Persistent growing tumor following simple mastectomy. Carcinoma is directly invading pectoral fascia and muscle and is present just beneath overlying skin (X3).

An additional 11 patients were found at Washington University who had radical mastectomy following simple mastectomy. Seven of these are now dead and 4 are living with disease. There was a high percentage of local recurrence in this group and all are destined to die of cancer.

DISCUSSION

In our series of cases noticeably better results were obtained in those patients wherein the delay from preliminary to final operation was not more

TABLE III. PATIENTS WITH PREVIOUS SIMPLE MASTECTOMY. RADICAL MASTECTOMY NOT COMPLETED

AGE (YR.)	ONSET OF SYMPTOMS TO SIMPLE MASTECTOMY	TIME FROM SIMPLE MASTECTOMY TO L.F.S.C.H. ADMISSION	LOCAL EXTENSION	AUXILIARY NODES	OTHER METASTASES	TIME FROM SIMPLE MASTECTOMY TO DEATH	TIME FROM L.F.S.C.H. ADMISSION TO DEATH
67	1 mo	48 mo	0	+	Inguinal, pul monary	63 mo	19 mo
50	0 mo	7 mo	Neuraxia	+	Supraclavicular	11 mo	4 mo
70	2 mo	20 mo	In scar	+	-	-8 mo	8 mo
51	8 mo	45 mo	Mass	+	Axillary nodes	60 mo	12 mo
72	0 mo	16 yr	Mass and skin nodules	0	-	19 yr	3 yr
39	0 mo	8 mo	Mass	+	-	10 mo	2 mo
41	2 mo	1 yr	Mass bilateral	Bilateral	-	10 mo	2 mo
60	0 mo	26 mo	Mass	0	Pleural effusion	13 yr	1 mo
35	2 mo	20 mo	0	0	Supraclavicular	40 mo	14 mo
78	4 mo	20 mo	0	0	Inguinal, pul monary	22 mo	2 mo
67	36 mo	11 mo	0	+	Axillary mass, skin nodules	22 yr	1 mo
60	2 mo	2 mo	Mass	+	Supraclavicular	13 mo	2 mo
69	4 mo	36 mo	Chest wall in vision	+	-	66 mo	64 mo
					Cervical	70 mo	20 mo

dence of axillary involvement and 3 of these had local recurrences (with muscle invasion etc.) as well. The final results in this group were notably poor even though the interval of time between simple and radical mastectomy was not unduly long. 4 with intervals of two months or less, and 2 with intervals of four and seven months, respectively. Fig 1, the photomicrograph, illustrates the typical picture of local recurrence following simple mastectomy.

The 9 patients who are living without evidence of disease all had intervals of two months or less. This emphasizes the importance of the short interval between initial biopsy and radical treatment. The prognosis was uniformly good in spite of the fact that 3 of these patients had persistent tumor in the pathologic specimen at the site of previous excision. It is significant that the size of the removed tumors was uniformly small. Seven of these patients were previously treated by local excision while the other 2 had previous simple mastectomies (see Table III).

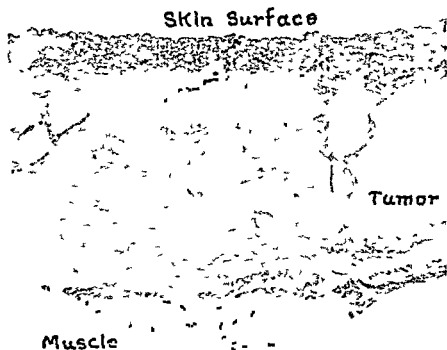


Fig 1—Persistent growing tumor following simple mastectomy. Carcinoma is directly invading pectoral fascia and muscle and is present just beneath overlying skin (X3).

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DISCUSSION

In our series of cases noticeably better results were obtained in those patients wherein the delay from preliminary to final operation was not more

TABLE III PATIENTS WITH ILLINOIS SIMPSON MASTECTOMY RADICAL MASTECTOMY NOT COMPLETED

AGE (YR)	ONSET OF SYMPTOMS TO SIMPSON MASTECTOMY	TIME FROM SIMPLE MASTECTOMY TO ILLINOIS ADMISSION		LOCAL PREF. PREC.	AXILLARY NOTES	OTHER METASTASES	TIME FROM SIMPLE MASTECTOMY TO DEATH		TIME FROM ILLINOIS ADMISSION TO DEATH
		1 mo	2 mo				1 mo	2 mo	
67	1 mo	45 mo		0	+	Inguinal, pul monary	63 mo		10 mo
40	9 mo	1 mo		+	+	Supraclavicular	11 mo		4 mo
70	2 mo	20 mo		+	Bilateral		28 mo		8 mo
51	8 mo	48 mo		+	In scar		60 mo		12 mo
72	6 mo	16 yr		+	Mass	Axillary, kin no Jules	19 yr		3 yr
39	6 mo	8 mo		+	Mass and skin no Jules				
47	2 mo	12 yr		+	Mass, bilateral	Bilateral	10 mo		2 mo
60	6 mo	20 mo		+	Mass	0	1 yr		1 mo
35	2 mo	20 mo		0	0	1 pleural effusion	40 mo		14 mo
48	4 mo	21 yr		0	0	Supraclavicular	22 mo		2 mo
67	36 mo	11 mo		0	+	Inguinal, pul monary	22 yr		1 mo
66	2 mo	2 mo		+	Mass	Axillary mass skin no Jules	13 mo		1 mo
61	4 mo	36 mo		0	0	Supraclavicular	66 mo		64 mo
				+	Chest wall in union	Cervical	26 mo		20 mo

dence of axillary involvement and 3 of these had local recurrences (with muscle invasion etc.) as well. The final results in this group were notably poor even though the interval of time between simple and radical mastectomy was not unduly long. 4 with intervals of two months or less, and 2 with intervals of four and seven months respectively. Fig 1, the photomicrograph illustrates the typical picture of local recurrence following simple mastectomy.

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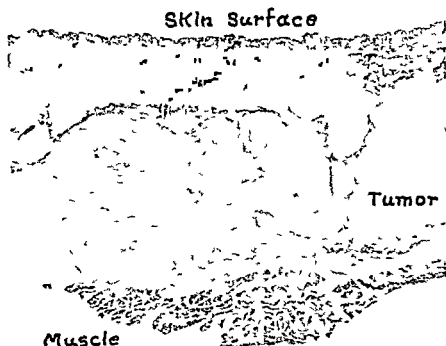


Fig 1.—Persistent growing tumor following simple mastectomy. Carcinoma is directly invading pectoral fascia and muscle and is present just beneath overlying skin ($\times 3$).

An additional 11 patients were found at Washington University who had radical mastectomy following simple mastectomy. Seven of these are now dead and 4 are living with disease. There was a high percentage of local recurrence in this group and all are destined to die of cancer.

DISCUSSION

In our series of cases noticeably better results were obtained in those patients wherein the delay from preliminary to final operation was not more

than two months. In fact all of our 9 patients living without disease had intervals limited to that period. In the patients who had previous simple mastectomy local recurrences frequently followed the subsequent radical operation. In the group of 13 patients with disease too far advanced for secondary radical operation, local and distant spread was a common finding. Furthermore the interval of time from simple mastectomy to death in those 13 patients (all now dead) was no longer than in those who were submitted to secondary radical operation. We ask then do radical operations performed after simple mastectomies actually hasten the death of the patient? A contributing factor in accounting for the prevalence of local recurrences following simple mastectomy might be the fact that in the performance of a simple mastectomy the amount of skin sacrificed is small relatively thick skin and subcutaneous tissue flaps are usually dissected (often cutting across strands of tumor which reach upward toward the skin surface) and that these flaps are then plastered down against denuded pectoral fascia providing an excellent bed for the growth of residual bits of tumor (Fig. 1). Also simple mastectomy is performed too often for larger tumors which are impossible to encompass by local excision. When radical mastectomy is performed for cancer following previous simple mastectomy a far more extensive and difficult operation is required. All of the area which has been previously undermined in the raising of the flaps in the first operation must be removed widely en bloc leaving a tremendous defect on the chest wall which necessitates the use of extensive skin grafts. In fact in our small group radical mastectomy following simple mastectomy did not prolong the life of a single patient. In the 2 patients who survived no tumor was found in the remaining breast or axilla so that apparently all the tumor was removed at the time of the first operation. These cases show that once simple mastectomy has been done for cancer the prognosis is extremely poor in practically every instance. On rare occasions however the surgeon may be lucky enough to remove all the tumor with the simple mastectomy. In our group this fortunate circumstance took place in only 2 out of 19 cases (9.5 per cent). The other 17 patients (91.5 per cent) are dead or dying. In spite of the fact that radical mastectomy following previous simple mastectomy did not change the prognosis in our group of patients we still must reluctantly recommend it inasmuch as the subsequent radical operation may rarely cure the patient. In the case of the patient who demonstrates clinically local recurrence and/or regional lymph node metastasis it is questionable whether radical mastectomy is indicated. In this group of cases irradiation might give better palliation.

Diagnostically simple mastectomy rarely provides more information than can be gained by simple biopsy of a tumor mass and unfortunately simple mastectomy occasionally introduces a temptation among some surgeons to temporize with the disease and to postpone further appropriate treatment.

Many human factors are responsible for the delay following biopsy which is so disastrous to the patient and even though the intentions of the physician are the very best he may be helpless in averting all extended postponement.

of radical treatment. Patients in general dislike the idea of two separate operations and would much prefer to have their trouble handled "at one sitting" not only for economic reasons but also in order to be relieved of the ordeal and associated anxiety. A patient's inertia with regard to his own welfare even when urged by his doctor is often a cumbersome influence. Also in certain areas admission to hospitals where radical operations can be performed may be hindered by waiting lists or lack of bed space. Undesirable lapses of time should be avoided at all costs if possible.

CONCLUSIONS AND RECOMMENDATIONS

1 Biopsy of breast tumors should be done judiciously and with facilities for subsequent radical mastectomy immediately available.

2 If it is necessary to delay the radical procedure after local excision the lapse of time before radical operation should be no longer than two months and certainly just as much sooner as is humanly possible.

3 Under no circumstance should simple mastectomy be employed as a diagnostic or therapeutic measure for an operable carcinoma of the breast. After such a procedure persistent carcinoma (as demonstrated by this series) almost invariably remains hidden in the operative field and/or axilla.

4 In 19 patients who had previous simple mastectomy in only 6 could radical mastectomy be completed and of these only 2 are living without disease. It is probable that in the patients who develop obvious local recurrence and/or regional lymph node metastasis after simple mastectomy radical mastectomy is contraindicated. Irradiation as a palliative procedure would probably be of greater benefit in this group.

5 In 22 patients who had previous local excision radical mastectomy was justified in 16 and of these 7 are living without disease.

REFERENCES

- 1 Adair F F. The Role of Surgery and Irradiation in Cancer of the Breast. *J A M A* 121: 553-559 1943.
- 2 Harrington Stuart W. Results of Radical Mastectomy in 50% Cases of Carcinoma of the Breast. *Pennsylvania M J* 43: 413-417 1940.
- 3 Greenough Robert B. Early Diagnosis of Cancer of the Breast. *Ann Surg* 102: 233-238 1935.
- 4 Siemen A. Die Prognose des Mammacarcinoma.
- 5 Slaughter K. For Simple Mastectomy. *Surg Gynec*.
- 6 Hicken. Mastectomy. Results in Incomplete Removal of Mammary Gland. *Arch Surg* 40: 614-619 1940.
- 7 Haagensen C D. Surgical Biopsy. Treatment of Cancer and Allied Diseases. George T. Park and E. M. Livingston. Chap. IV. Vol. 1. New York 1940. Paul P. Hoelzer Inc. p. 4-51.

CANCER OF THE RECTUM

HARRY E. BACON, M.D. PHILADELPHIA, PA.

THE cardinal objective in dealing with a cancerous lesion is to eradicate the disease process, and it is recognized that this can be achieved only by wide removal of the growth and all gland bearing tissues. Methods designed solely for reasons of sentiment at the expense of survival of life should be deleted from our surgical armamentarium. Obviously no surgeon of sound mind would deliberately or maliciously perform a procedure of limited scope for a resectable malignancy of the rectum if by such procedure recurrence would reasonably be expected to occur and the period of survival thereby curtailed.

The classical and popular type of extirpation is that devised by Miles—the method of abdominoperineal excision. I am frank to admit that if there were available but one operation for rectal cancer my unqualified choice would be the Miles' procedure. Nearly twenty years devoted to bowel surgery have convinced me that any surgeon dealing with rectal and sigmoidal cancer in large numbers must have several methods at his disposal, methods not only with which he is acquainted but which he is capable of performing well. Our chief concern must be the individual patient; therefore the commission of that common surgical sin of adapting the patient to the operation rather than the procedure to the patient should be avoided. Time upon time during the course of my experience an alternate technique has been justified. While all of us today lean very decidedly toward single stage resection, graded procedures must never be deleted entirely. The exteriorization method of Mikulicz and Rankin for sigmoidal growths, as well as colostomy and posterior excision (Lockhart Mummery), and the two stage Lahey-Cattell abdominoperineal excision for lesions of the anorectum have definite value in some instances. Owing to various factors intervening during the course of the operation the seasoned operator may wisely select an alternate method. For these reasons we are constrained to take issue with such a statement as "There is only one operation for cancer of the rectum, namely the Miles' procedure."

Contrary to common belief we in our department do not condemn the Miles' procedure, evidence of which is the frequency of its performance in our department, but its use is confined to selected cases. On the other hand we do not sanction a perineal colostomy in which the anal sphincters are sacrificed for the sole purpose of avoiding an abdominal stoma. We are emphatically critical of and unalterably opposed to the frequency with which an abdominal colostomy is established not only by the occasional operator but by those who are extirpating these growths in a large number of cases. Regrettably the old axiom "when in doubt do a colostomy" has not but should

be, relegated to the limbo of the forgotten past. It is common knowledge that a permanent abdominal colostomy is performed much too often, particularly in the presence of inoperable malignancy without obstruction. While not common knowledge it is my honest contention that the establishment of an abdominal stoma and sacrifice of the sphincter musculature is needlessly instituted in a far greater percentage of cases than is indicated or required. These remarks should in no way be construed as if it has been intended to imply that the ideal solution has been achieved. But little has been contributed and possibly nothing of particular import but like others, there is a striving for a method 'par excellence' yet to be designed.

Interest during the past several years while centering around all phases of lower bowel malignancy has dealt chiefly with the surgical management of malignant lesions in various segments of the lower bowel. Thus an opportunity has been afforded to investigate and re-evaluate the results both immediate and remote of methods employed to eliminate abdominal colostomy, particularly in the procedure advocated and popularized by Babcock in 1932^{1,2} and in his subsequent publications^{3,4}. This method with which I have had some experience is described under the term proctosigmoidectomy, but sometimes is referred to as the over and under or pull through method.

Investigations in our department while by no means exhaustive have been directed toward various phases of the technique but particularly toward the determination of the soundness and practicality of the procedure. For example it was found that transplantation of the iliac sigmoid could be readily achieved anatomically and viability could be maintained by precise division of the sigmoidal vessels and preservation of the communicating arcades. This has been reported by Smith and the author⁵. It was observed that in a group of 146 consecutive cases the average length of bowel removed by this operation was 29.6 cm. which is approximately the same amount as that excised by the Miles' method. Measurement at the point of arterial ligation averaged from 38 to 55 cm. from the coccyx tip whereas with the abdominoperineal method of excision Gabriel recorded an average distance of 25 cm. It is recognized that the removal of an extended length of bowel is desirable because of the frequency with which additional lesions are encountered. Only last year we⁶ reported a series of 171 consecutive patients on whom an abdominoperineal proctosigmoidectomy had been performed for cancer. Fifty-four (31.2 per cent) presented a concomitant adenoma in the removed specimen eleven (20 per cent) of these concomitant adenomas showed malignant degeneration.

Radicality implies extirpation of the cancerous bowel and wide removal of the gland bearing areas. The chief concern was to determine the degree of radical extirpation obtainable by the method used. It was found that during the abdominal phase tissue overlying the iliac vessels (upper mesocolon) was removed by a combination of sharp dissection and gentle separation as far as the bifurcation of the aorta. Included were those node bearing areas throughout the mesosigmoid and around the superior hemorrhoidal vessels. Likewise a wide expanse of mesorectum with its lower mesocolic nodes in

sigmoidectomy without colostomy and with preservation of the sphincter musculature was performed on 401 cases

TABLE I AUTHOR'S SERIES TABLE OF THE PROCEDURES

PROCEDURE	NUMBER OF CASES	DEATHS	MORTALITY (PER CENT)
1 Sigmoidectomy (end to end anastomosis Mikulicz Rankin, Hartmann)	90	8	8.8
2 Abdomino-perineal proctosigmoidectomy	401	0	4.1
3 Abdomino-perineal extension (Miles, Lahey Lockhart Mummery)	14	0	2.7
4 Perineal resection (Cunéo Seneque)	2	0	0
Total	647	33	5.1

SUMMARY

A personal series of 800 patients with malignancy of the lower bowel on whom radical resection was performed in 638 instances serves as a basis for comment. Excision by the abdomino-perineal method with the establishment of a permanent abdominal stoma preferably by the method of Miles is recommended for all growths involving the anal canal and lowest 3 cm. of the rectum, and very definitely no attempt should be made to preserve the sphincter musculature for lesions in this area. Cancerous processes cephalad to this site may be removed by the procedure designated by Miles although our preference is proctosigmoidectomy. Those who manifest interest and wish to master the technique of proctosigmoidectomy will find it a method suitable for ampullary growths of the rectum, the rectosigmoid and the terminal pelvic colon. An experience of eight years during which period this method was employed in a group of 401 patients with cancer provides evidence that the operative mortality rate is low, the period of morbidity diminished and the five year rate of survival parallels and in some instances, is better than that obtained by the Miles and other procedures. The incidence of local recurrence is greater by less than 2 per cent, using the exhaustive investigations of Gilchrist for comparison. Sexual impotence in the male is decreased and anal sphincter function is satisfactorily uniform. If and when the statistics evidence the fact that the results in a larger group of patients than is now available and particularly the ten year rate of survival do not compare favorably with those achieved by other methods then shall the error be acknowledged and the procedure completely deleted from the surgical armamentarium.

As Wangenstein has aptly stated "we cannot resolve our differences by debate but rather by analyzing our experiences critically and recording them truthfully. Time is the final arbiter of all things. Until she has given her answer let us be tolerant of our honest differences of opinion."

REFERENCES

1 Babec

2 Babec

3 Babcock W. W. The Advantages of Perineal Over Abdominal Colostomy With Technique for Transferring the Abdominal Opening to Perineum. J. A. M. A. 113: 1933

1933

- 4 Babcock, W W The Symptoms and Operative Treatment of Carcinoma of the Large Bowel With a Method for the Elimination of Colostomy South Surgeon 1 260, 1933
- 5 Babcock W W Symptoms and Diagnosis of Carcinoma of the Colon With a New Method for Extirpating the Rectosigmoid Pennsylvania M J 36 180 1932
- 6 Lewis & Co Ltd Printed in Great Britain
- 9 P
- 10
- 11
- 12
- 13 With Particular Reference to Cancer and Ulcerative Colitis Am J Surg 75 384 1948
- 14 Bacon H F and Rowe R J Primary Resection for Cancer of the Lower Bowel, New York State J Med 48 607 1948
- 15 Bacon H F and Vaughan G D Abdominoperineal Proctosigmoidectomy Incidence of Local Recurrence Ohio State M J 45 807 1949

sigmoidectomy without colostomy and with preservation of the sphincter musculature was performed on 401 cases

TABLE I. AUTHOR'S SERIES, TABLE OF THE PROCEDURES

PROCEDURE	NUMBER OF CASES	DEATHS	MORTALITY (PER CENT)
1 Sigmoidectomy (end to end anastomosis Mikulicz Pankin Hartmann)	90	8	8.9
2 Abdominoperineal proctosigmoidectomy	401	20	5.0
3 Abdominoperineal excision (Miles, Lahey Lockhart Mummery)	143	3	2.1
4 Perineal resection (Cunéo Seneque)	2	0	0
Total	634	31	4.9

SUMMARY

A personal series of 800 patients with malignancy of the lower bowel on whom radical resection was performed in 638 instances serves as a basis for comment. Excision by the abdominoperineal method with the establishment of a permanent abdominal stoma preferably by the method of Miles, is recommended for all growths involving the anal canal and lowest 3 cm. of the rectum, and very definitely no attempt should be made to preserve the sphincter musculature for lesions in this area. Cancerous processes cephalad to this site may be removed by the procedure designated by Miles, although our preference is proctosigmoidectomy. Those who manifest interest and wish to master the technique of proctosigmoidectomy will find it a method suitable for ampullary growths of the rectum, the rectosigmoid and the terminal pelvic colon. An experience of eight years during which period this method was employed in a group of 401 patients with cancer provides evidence that the operative mortality rate is low, the period of morbidity diminished and the five year rate of survival parallels and in some instances is better than that obtained by the Miles and other procedures. The incidence of local recurrence is greater by less than 2 per cent, using the exhaustive investigations of Gilchrist for comparison. Sexual impotence in the male is decreased and anal sphincter function is satisfactorily uniform. If and when the statistics evidence the fact that the results in a larger group of patients than is now available and particularly the ten year rate of survival do not compare favorably with those achieved by other methods then shall the error be acknowledged and the procedure completely deleted from the surgical armamentarium.

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REFERENCES

1. Babo
2. Babo
3. Babo

below the diaphragm Roscoe Graham went so far as actually to obstruct the jejunal lumen in this attempt though providing an adequate by passing of duodenal contents Yet his mortality records demonstrated no obvious improvement

The historical evolution of these operations has been thoroughly discussed in previous publications Except for the supra aortic esophagogastrostomy they had all been attempted on numerous occasions by Sauerbruch Wendel, etc Unquestionably the real credit for their successful adoption must go to Carlock Pack and Sweet who have standardized these procedures and made them safe and feasible Carlock not only revived this field of surgery but extended the operation of esophagogastrostomy to resection of esophageal cancers above the aortic arch The gradual adoption of Sweet's technique of esophageal anastomosis has been one of the most important factors in the successful performance of esophagogastrostomy for there is no other procedure which demands such meticulous attention to every detail at each stage of a long surgical seance Frequently after a fatiguing tedious dissection of the tumor the operator would welcome the completion of the operation by another surgeon Yet the care with which the anastomosis is constructed determines the success of the entire procedure There can be little question that a fall in medical complications invariably follows the attainment of a sound surgical technique Conversely there is probably no other group of procedures of which it may be said with greater truth that the operation is merely an incident in the management of the disease

Preoperative Care—Factors governing the correction of the starvation state which all too frequently affect these patients have been widely and repeatedly elaborated in surgical and medical literature An intelligent application of the principles of establishing a positive nitrogen balance wherever possible the restoration of electrolytes water balance and vitamin replacement is taken for granted It has not been necessary to perform jejunostomy preoperatively in a single instance in fact we doubt if the occasion need arise at all It should be avoided at all cost as the jejunum may well be required in the anastomosis An estimation of the vital capacity an electrocardiogram a film of the lungs and a urine concentration test comprise the list of special examinations preoperatively Regardless of all the recent studies in the use of protein substitutes let it be said here and now that in my opinion there is no substitute for blood transfusion in the pre and postoperative phase as well as during the operation itself

Operative Technique—The patient is placed either in the supine or right lateral decubitus position depending on whether the procedure is to be performed above or below the diaphragm Where the possibility of laparothoriotomy -
five degrees -
for cancers -
of total -
the expo

PRINCIPLES AFFECTING SUCCESSFUL ESOPHAGEAL ANASTOMOSIS

A REPORT OF TWENTY THREE OPERATIONS WITHOUT OPERATIVE MORTALITY

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THE time is apparently at hand when resections and anastomoses involving the esophagus are as safe as those associated with any other organ. As recently as June, 1948, published hospital mortalities for such operations were generally in the neighborhood of 30 to 35 per cent. There seems little reason to doubt that present methods will improve even further. Textbooks cannot keep pace with the many improvements and advances which have made possible vastly better operative techniques and end results. From the early days when subtotal gastrectomy was performed with mortalities ranging from 50 to 75 per cent in the best of hands to the present day when the occasional death from the operation is the result of factors presently not under the control of the surgeon, has been a relatively short time. The gradual standardization of surgical techniques and training, advances in anesthesiology, and the science of nutrition have all played their part in the accomplishments of this present day. Yet it is not at all unlikely that operative deaths which today we consider as beyond the realm of surgical and medical control, will at some future time be prevented with the same ease as the once feared pulmonary atelectasis. To digress from the gastrointestinal field for a moment the present successful revival of the Wertheim operation for cancers of the uterus is an excellent illustration in point.

Although the successful adoption of many of our surgical techniques has required many years the really astounding improvements in operative mortalities after esophageal anastomosis have been brought about in less than ten years. For during this short period of time the operations of total gastrectomy, resection of the gastric cardia and esophagectomy have become standardized. Perl and McNeer reviewed the literature of all published total gastrectomies in 1943 including twenty cases of their own and found an operative mortality averaging well over 33½ per cent under the best of circumstances. The causes of death were in the main the result of peritonitis, bronchopneumonia and heart failure. Since post mortem examinations were not granted in all instances the exact state of the esophageal anastomosis could not always be determined. The significant fact remains however that when an autopsy was performed peritonitis was all too often encountered. Likewise fistulas occurred in a high percentage of cases (30 to 40 per cent). Interestingly enough we have all been made aware of the change in physical findings in peritonitis resulting from chemotherapy and antibiotic agents.

Numerous operative techniques were devised to protect buttress and support the esophageal anastomosis with jejunum or stomach both above and

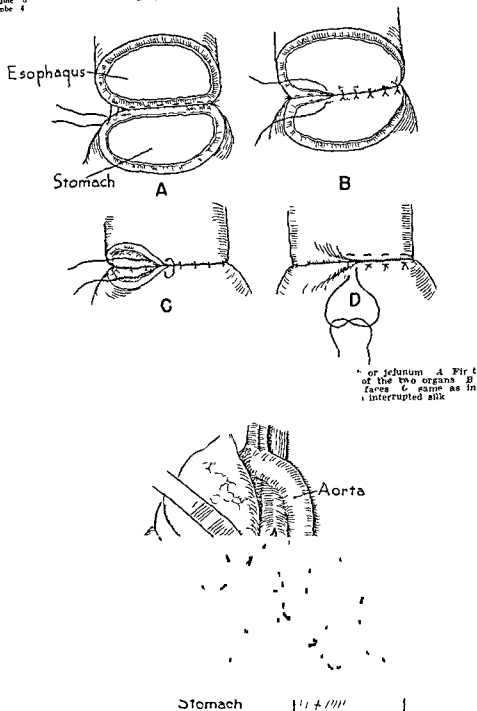
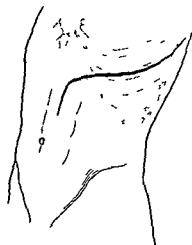


Fig 3—Esophagogastrotomy after resection of the gastric cardia suture of operative site to mediastinal pleura

so greatly enhanced as to make up for the additional surgical shock and extended operative time required for wound closure

A fact that is not adequately appreciated by most abdominal surgeons of even great experience is that far greater surgical shock attends operations in the upper abdomen via laparotomy and especially laparothoracotomy as opposed to thoracotomy. The smoothness of the postoperative phase with particular regard to intestinal stasis is incomparably superior after thoricotomy. If the lesion is in the region of the diaphragm there is no need or excuse for laparotomy. As Sweet has pointed out time and again in his communications there can be no possible advantage in approaching either carcinoma, diverticulum, ulcer or hernia in this region by any other route. As he stated most aptly it would be analogous to attempt to repair a large inguinal hernia through a laparotomy incision. The needless fear of thoricotomy held by most general surgeons impels them to employ laparotomy. The successful management of the spleen through the open thorax is especially gratifying



A F

Fig. 1—Incision for laparothoracotomy (From Pack and McNeer, *STRAFF* 1943)

It is believed that resection of a rib rather than intercostal spreading and fracture is preferable because exposure is superior, the wound closes more easily and is less painful postoperatively.

Since appreciating the remarkable advantage of laparothoracotomy for total gastrectomy, all patients undergoing gastric operations for cancer are preferably anesthetized by intratracheal ether. It is never possible to tell from studies of x-ray films how high a resection may be required. Hence when performing gastrectomy for cancer spinal anesthesia is not advised. It is very comforting to know that the incision may be extended into the thorax when necessary. Clamps are never to be placed across that part of esophagus subsequently to be used in the anastomosis.

order to prevent subsequent stricture. A continuous inner layer of catgut tends to act as a purse string, and thus obstructs the lumen. Though the employment of an interrupted fine silk technique may be time consuming, the results justify it in the long run. A definite point is made to insert sutures at right angles to the esophageal musculature always in through and through fashion. The integrity of the anastomosis depends on this principle more than any other. If in addition, the esophagus is not dissected enough proximally to require ligation of any of the vessels supplying it with blood, there should be no concern regarding its integrity.

Retraction of the wound edges is vital if adequate exposure is to be obtained, yet it must be cautiously employed. Frequently in the past the retractors have been applied in too close approximation to the heart, particularly if the diaphragm has not been opened during total gastrectomy. Serious cardiac changes have been observed which tended to compromise both the operative and postoperative phase. Since recognizing this danger, the retractors are never placed in such a position that they may forcefully compress the heart either above or below the diaphragm. The lessening of unfavorable cardiac reflexes and the tendency toward shock have been especially gratifying.

Fixation of the anastomosis to adjacent structures promotes wound healing by immobilization of the operative site. The infradiaphragmatic anastomosis must be sutured to diaphragm, hepatic ligament or left lobe of liver depending on which is closest to the suture line. When constructed within the thorax the entire segment of stomach or intestine must be carefully sutured to diaphragm and preaortic pleura. In this way the entire anastomosis is in fact buried in the mediastinum.

We have observed that since the underwater drainage tube has been placed just within the thorax and not down close to the anastomosis the occurrence of fistula has ceased.

Postoperative Care—Though the trachea has been aspirated at the termination of the operation and the lungs frequently re-expanded, the tendency to postoperative pulmonary atelectasis is still great. The most important single contribution toward the lessening of serious postoperative pulmonary complications has been the frequent aspiration of the trachea by the house staff. This is performed on the evening of the operation and twice daily thereafter until the patient is capable of raising the sputum himself. In addition, blow bottle carbon dioxide rinsing and intramuscular injections of penicillin are employed prophylactically. Since ligating the superficial femoral veins preoperatively, pulmonary embolus has not occurred.

Too great emphasis cannot be placed on the value of postoperative tracheal aspiration. Since its adoption in all instances of high gastric and esophageal resections, there have been very few serious pulmonary complications.

Indwelling Pharyngeal Tubes—The use of indwelling nasal tubes for feeding purposes is greatly to be deplored. The tendency toward fatal pulmonary

Regardless of whether esophagus is anastomosed to stomach or jejunum the adoption of an interrupted nonabsorbable suture in two or three layers as advocated by Sweet is absolutely fundamental to the success of the procedure. Meticulous apposition of the mucosal surfaces must be observed in

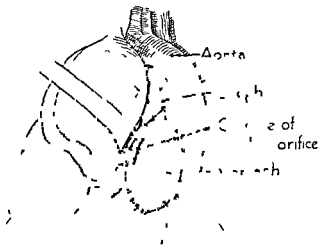


Fig 4—Esophagogastrostomy after resection of the mid esophagus

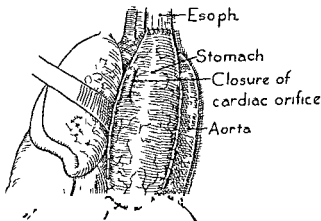


Fig 5—Supra-aortic esophagogastrostomy

PATIENT CASE AND AGE	OPERATION	DIAGNOSIS	COMPLICATIONS	END RESULT
15 S 63	Trans thoracic resection of gastric cardia and e ophagoga tros tomy 3/-3/48	Adenocarcinoma of stomach, Grade II, with lymph node metastasis	None	Living and well
16 C L 36	Abdominothoracic total ga trectomy and esophagojuno tomy 4/-4/48	Gelatinous adeno carcinoma of stomach	None	Living and well
17 C S 57	F ophagectomy and e ophagoga tros tomy 4/-1/48	Epidermoid car cinoma of e ophagus with metastasis to liver	None	Living and well
18 M D 59	Trans abdominal re sec tion of the gastric cardia e ophagoga tro tomy and gastro entero tomy 6/-2/48	Peptic ulcer	None	Dis charged
19 J M 49	Trans thoracic re section of the gastric cardia and e ophagoga tro tomy 6/12/48	Adenocarcinoma of stomach Grade III in filtrating gastric wall metastases to lymph nodes	Pleural effusion	Dis charged
20 J S 54	Trans thoracic total ga trectomy e opha gojejunotomy and jejunajejunostomy 6/-2/48	Adenocarcinoma of stomach with lymph node meta ta is	None	Dis charged
21 A W 69	Trans abdominal total ga trectomy esopha gojejunotomy and jejunajejunotomy 7/1/48	Adenocarcinoma of stomach with lymph node metastasis	None	Dis charged
22 J E 61	F ophagectomy and e ophagoga tros tomy 7/-0/48	Epidermoid car cinoma of esophagus with meta ta sis to right cervical lymph node	None	Dis charged on full diet
23 P B 71	F ophagectomy and esophagoga tros tomy 8/3/48	Leiomyosarcoma of e ophagus	None	Discharged on full diet

1 Total gastrectomy and esophagojejunostomy for cancer of the stomach	9
2 Resection of gastric cardia and esophagogastricostomy } for cancer	5
3 " "	2
	4
	1
	1
All cases per cent	1
Total number of operations	23

TABLE I ESOPHAGEAL LESIONOMES SUMMARY OF CASE HISTORIES

PATIENT					
1					
2	S L 69	Abdominotheracic total gastrectomy and esophagojejunos tomy, 5/1/47	lymph node me- tastasis Adenocarcinoma of stomach with lymph node me- tastasis	None	Died of metastasis, 11/17/47 (6 mo)
3	L M 50	Abdominal resection of	Adenocarcinoma	Transient diarrhea	Died December 1947 (8 mo)
4	D 40				Died 8/5/47 (3 mo)
5	A P 39	Transabdominal total gastrectomy and esophagojejunos tomy, 8/12/47	Adenocarcinoma of stomach with lymph node metastasis	None	Living with me- tastasis (8 mo)
6	C R 39	Trans thoracic resec- tion of gastric cardia and distal	Peptic ulcer	None	Living and well
7	A 58			Atelectasis broncho- pneumonia	Living and well
8	D 39			Pleural effu- sion	Operative sur- vivor cancer found at time of resection
9	D 9	Trans thoracic esopha- gectomy and jejunec- tomy and esophago- jejunostomy, 1/6/48	Adenocarcinoma of stomach with lymph node metastasis	None	Living and well (5 mo)
10	F Z 52	Abdominal total gas- trectomy and esopha- gojejunostomy, 12/13/47	Colloid carcinoma of stomach with lymph node metastasis	Intestinal ob- struction re- quiring lip- nectomy	Living and well (5 mo)
11	A B 33	Trans thoracic resection of gastric cardia and esophagoje- junostomy, 12/10/47	Adenocarcinoma of stomach Grade II with lymph node metastasis	None	Living and well
12	A M 30	Trans thoracic esopha- gectomy and jejunec- tomy, 1/4/48	Cardiovascular	None	Living and well
13	M M 41	Trans thoracic total gastrectomy and esophagojejunos tomy, 3/9/48	Adenocarcinoma of stomach Grade II with lymph node metastasis	Pleural effusion	Operative sur- vivor laparot- omy for obstruc- tion due to re- currence 5/19/48
14	F K 34			Pleural effusion	Living and well (usual re- currence of gas- tric tumor)

therapy in 1942. In 1948 symptoms denoting obstruction at the gastroenterostomy demanded laparotomy, at which time the remaining stomach, upper jejunum, and transverse colon were resected and the appropriate anastomoses constructed. Pathologic study of the resected specimen revealed gelatinous adenocarcinoma of the gastric remnant invading the stoma of the gastrojejunostomy and the transverse colon. No explanation of this astounding pathologic entity has been offered by the pathologist. Sixteen patients underwent resection for adenocarcinoma of the stomach, four for epidermoid cancers of the esophagus, one for leiomyosarcoma of the esophagus, and two for benign gastric ulcer. Esophagogastrostomy was performed for refractory cardiospasm in one instance (Table II). Interestingly enough two total gastrectomies for carcinoma were performed on men in their mid thirties for lesions suspected preoperatively both clinically and radiographically, of being benign gastric ulcers. Likewise resection of the cardia was carried out on one individual for an enormous ulceration of the cardia involving spleen, tail of pancreas, diaphragm and left lobe of liver which proved to be peptic in origin. Esophagectomy was performed on one patient (Case 22) in spite of the presence of a metastasis to the liver and in another patient in the face of a metastasis to a cervical lymph node. It was thought that they might thereby be offered far more palliation than by gastrostomy. Two weeks postoperatively they were enjoying a regular diet. The resection of readily mobile obstructing cancers of the esophagus in the presence of distant metastases must therefore be placed on a basis comparable to the management of similar lesions elsewhere in the gastrointestinal tract.

All patients are carefully studied fluoroscopically after barium swallowing and a few x-ray films made of the anastomotic site, prior to discharge from the hospital. This study affords a valuable comparison for the future in the event that stenosis does occur.

Our short experience with secondary operations for recurrent gastric and esophageal cancer thus far suggests that such lesions may be successfully resected more often than we realize.

Pulmonary complications were remarkably infrequent and mild as a result of the measures suggested in this communication.

RESULTS

This study covers a period of slightly over one year and hence results may not properly be evaluated. Undoubtedly some of these patients will remain well. Some have already died and others will likewise do so.

In the absence of distant metastases there is no known method by which the operating surgeon may differentiate between the patient who will soon die of recurrence and the long term survivor. Hence all operable lesions must be resected. It is peculiarly pertinent to observe one patient (Case 13) who having undergone transthoracic total gastric resection was found to have carcinoma infiltrating the proximal line of resection. Esophageal obstruction soon intervened requiring thoracotomy a second time. When cancer was found to invade the anastomosis it was resected en bloc and esophagus re-

complication thereby has been demonstrated conclusively. In addition, the patient is made just that much more uncomfortable. When one sees the slime and filthy debris clinging to an indwelling tube after one week's intrapharyngeal residence one cannot help but be impressed with the higher frequency of pneumonia attendant on its use.

Oral Feeding—Of possibly still greater importance is rejection of the heresy which has governed the optimum time for feeding these patients. As soon as peristalsis is heard in the abdomen (twenty-four to forty-eight hours) the patient is given water and tea by mouth. Clear liquids are given as tolerated in ever-increasing amounts so that by the seventh to tenth day the patient ingests a soft diet. This method has numerous advantages. First of all the patient is delighted and encouraged beyond imagination. Second, the saliva produced in large amounts daily is diluted and cannot so readily cling to the edematous borders of the anastomosis. Third the necessity for continuing parenteral fluids rapidly decreases so that by the fifth day all feeding is by mouth as a rule. The tendency toward intolerance of parenteral fluids in large amounts by elderly subjects has strengthened the attitude in regard to limiting parenteral fluids. It was observed that these subjects often tolerate 2000 cc of glucose and water daily more readily than the 3000 to 5000 cc as previously employed. There is far less tendency toward electrolyte failure if such patients have a daily urinary output of 1000 cc rather than 2000 cc. What is probably equally important is that the urinary specific gravity more nearly approaches normal as a result thus indicating an improved water balance. Most interesting of all is that these individuals have usually regained their preoperative weight by the fourteenth postoperative day and are ready to go home—at a time when most surgeons are just beginning to permit them oral feedings.

Formerly an auxiliary jejunostomy was constructed for feeding purposes. This has been abandoned as a result of the good effects of early oral feeding. The high frequency of diarrhea and occasional intestinal obstruction have likewise militated against jejunostomy.

There seems to be no indication in any of these patients adequately prepared for operation that hydrolyzed protein feedings in the postoperative phase offered any material assistance. In fact the tendency toward bloating, distress, nausea, and diarrhea was greatly enhanced. Transfusion of whole blood and supplementary oral feedings of a diet high in protein were far more efficacious.

Material—The cases of twenty-two patients upon whom were performed twenty-three consecutive anastomoses involving the esophagus without hospital mortality form the basis of this study (Table I). Fistula did not occur in a single instance. Stricture of the anastomotic site occurred on five occasions, the result of recurrent cancer in all instances permitting reoperation and successful resection in one.¹¹⁻¹⁴ In Case 19 a 34-year-old patient had undergone subtotal resection in 1941 for a gastric lymphosarcoma. Recurrence in the operative incision required protracted high voltage x-ray

TRAUMATIC ILIAC HERNIA WITH EXTENSIVE SOFT TISSUE LOSS

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HERNIAS through natural foramina of the pelvis such as sciatic and obturator have been repeatedly described. However herniation of the intestines through an artificial aperture in the iliac wing is a sequel to a comminuted fracture has not attracted much attention in the voluminous literature on hernia.

Extensive comminution of the ilium leading to the development of a permanent and substantial defect is quite unusual but does occur particularly in military traumatology as a result of destruction due to gunshot wounds. Such bony defects represent potential channels for herniation of the pelvic content. Ordinarily the powerful muscular mass overlying the ilium offers additional protection. If this soft tissue pad is also destroyed a herniation of the intestines is an obvious sequel. When the defect involves the left ilium the nearest intestinal segment is the descending colon or its portion often described as iliac colon.*

As a rule the mobility of the descending colon is limited by its attachment to the peritoneum. However in 16 per cent of cases (according to TREVS) the descending colon has a well developed mesocolon. In such an instance when an opening in the pelvic wall exists adjacent to the colon the intra abdominal pressure will force a fragment of the colon out of the pelvic cavity as much as the length of the mesocolon will permit and a hernia will result.

Oldfield described a case of a cecal hernia through a defect in the right ilium which developed after quarrying bone grafts from it repeatedly. The surrounding soft tissues were essentially intact except for the surgical trauma.

The two most important principles of any hernioplasty are first elimination of any niche on the internal surface second utilization of dynamic structures. The pressure of an intra abdominal organ will act like a wedge against a depression in the abdominal wall and ultimately weaken the outer structures. Inactive tissue alone such as fascia is unreliable for permanent repair. A satisfactory closure should include a dynamic blockade of muscle or fascia held tense by muscle preferably forming the internal wall. Obliteration of a large defect in the iliac wing can best be done by utilizing adjacent soft tissues muscle periosteum etc. if sufficient material is available locally to accomplish a multi layer suture. If this is not the case the closure may be

anastomosed to a jejunal loop. The successful conclusion of this procedure has greatly altered our point of view regarding recurrent gastric and esophageal cancer and brought forward two suggestions:

- 1 Always resect for recurrent cancer if no distant metastases are demonstrable
- 2 Submit the proximal portion of all esophageal resections to frozen section delaying anastomosis until pathologic study has been completed

An interesting fact is that six of these operations have been conducted at a relatively small county hospital for the first time. The success gained in their performance has been the direct result of the inescapable conclusion—that these operations can be performed in any good hospital provided that in addition to the surgeon, there is provided good anesthesia, good nursing and the intelligent follow up care of a well trained resident surgeon. Constant vigilance and meticulous attention to the innumerable minutiae of post operative management are invariable requirements at all times. There is no doubt but that these procedures will be performed with ever increasing frequency in smaller institutions as these conditions obtain more widely.

SUMMARY AND CONCLUSIONS

- 1 Experiences with twenty three consecutive esophageal anastomoses without hospital mortality are recorded
- 2 Principles regarding the minutiae of postoperative care are stressed
- 3 Early oral feeding is advised
- 4 Exploration of recurrent gastric and esophageal cancer is suggested
- 5 Resection rather than gastrostomy as a palliative procedure is proposed for readily mobile obstructing esophageal cancers associated with distant metastasis

REFERENCES

- Garlock J. H. *Surgical Treatment of Carcinoma of Thoracic Esophagus* Surg. Gynec. & Obst. 80: 1010 (1945)
- Garlock J. H. *The Continuity Following Resection of the Esophagus* J. Surg. Gynec. & Obst. 78: 2328 (1944)
- Mauer I. *End Results of Esophageal Resection and Post Operative Care in Esophageal Cancer* Surg. Gynec. & Obst. 77: 1010 (1943)
- Park G. *Surgical Treatment of Cancers of the Gastric Cardia* STREETER 23: 95 (1948)
- Strieder H. *The Treatment of Carcinoma of the Esophagus and Cardiac End of the Stomach by Surgical Extirpation* SURGERY 23: 95 (1948)
- Sweet I. H. *Ann Surg* 121: 272 (1945)
- Sweet I. H. *The Treatment of Carcinoma of the Esophagus and Cardiac End of the Stomach by Surgical Extirpation* SURGERY 23: 95 (1948)

CASE REPORT

A 31 year old soldier was injured by a fragment of mortar shell in action in France on July 31, 1944. He suffered a compound comminuted fracture of the left iliac wing with extensive loss of soft tissues in the left flank. He was treated at various places along the chain of evacuation and on Aug. 29, 1944 while in a numbered General Hospital overseas an attempt was made to resurface the soft tissue defect with contiguous flap. However, because of a partial necrosis of a delayed flap this plan was abandoned and the wound covered with a temporary split graft. In October, 1944 he was evacuated to the United States. On Feb. 10, 1945 he was admitted to Cushing General Hospital.

Examination on admission revealed a short stocky rather obese patient with an extensive defect, 10 by 8 inches in the left flank along the posterior crest of the iliac bone and over the acetum (Fig. 1). The loss involved skin, subcutaneous and muscular structures. The area was covered with a scar and thin skin graft which for the most part were adherent to the underlying bone. Posterior to the anterior iliac spine there was a defect in the ilium admitting a thumb. Protruding from this defect was a thin walled hernial sac which spread to a girth of 3½ inches in diameter. The sac was covered with a thin skin graft. The hernia bulged on coughing and was easily reducible. Pressure on the hernial sac gave the patient a sensation of desiring to defecate.

A triangular flap 3 inches wide at its tip was outlined along the upper border of the scarred area. Originally it extended almost to the spine but its distal 4 inches had sloughed and were replaced by a skin graft. Another flap was outlined over the lower part of the buttock based along the periphery of the anus.

X-ray examination of the pelvis showed a comminuted fracture of the left wing of the ilium with loss of substance in the upper portion of the defect. A fracture line extended from the defect down to just above the superior margin of the acetabulum. The anterior iliac fragment was rotated anteriorly and lifted downward. Another fracture line extended into the sacroiliac joint. Radiographic examination after a barium enema demonstrated the herniation of the descending colon (Fig. 2).

The patient wore a canvas corset and by using crutches was able to walk only a few steps. He complained of instability of his pelvic frame and the sensation that his "innards" were falling out.

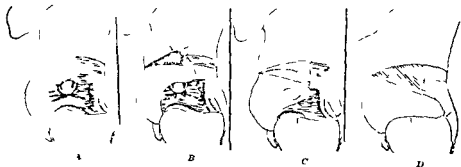


Fig. 3 A, B, C and D—Diagram depicting successive migration of flap.

The main feature of this case was a large intestinal hernia through a narrow rigid aperture in the iliac wing. This was associated with complete loss of the overlying soft tissues including skin.

The plan for resurfacing was complicated greatly by the loss of a considerable portion of the previously delayed flap. The remaining flap was obviously too small to be shifted directly into the desired position. The skin

attempted by using a large sheet of fascia lata, tantalum mesh or plate or a bone graft. The presence of intact skin and subcutaneous tissue is an essential requirement for any successful closure of a bony defect, whatever the procedure. If the surrounding soft tissue is lost and the skin is scarred or replaced by free skin grafts, resurfacing with a thick skin flap must precede any attempt to close the defect. The flap should not be limited to the size of the bony aperture, but should extend beyond it on all sides.

The case described here presented extensive destruction of both bone and soft tissues and offered a combined problem of resurfacing and obliteration of a large opening in the diaphragm.



Fig. 1—Condition on admission, note bulging hernia.



Fig. 2—X-ray showing the double-broasted hernia of the colon.

CASE REPORT

A 31 year old soldier was injured by a fragment of mortar shell in action in France on July 31, 1944. He suffered a compound comminuted fracture of the left iliac wing with extensive loss of soft tissues in the left flank. He was treated at various places along the chain of evacuation and on Aug. 29, 1944 while in a numbered General Hospital overseas an attempt was made to reurface the soft tissue defect with contiguous flaps. However because of a partial necrosis of a delayed flap this plan was abandoned and the wound covered with a temporary split graft. In October 1944 he was evacuated to the United States. On Feb. 10, 1945 he was admitted to Cushing General Hospital.

Examination on admission revealed a short, stocky rather obese patient with an extensive defect 10 by 8 inches in the left flank along the posterior crest of the iliac bone and over the sacrum (Fig. 1). The loss involved skin, subcutaneous and muscular structures. The area was covered with a scar and thin skin grafts which, for the most part were adherent to the underlying bone. Posterior to the anterior iliac spine there was a defect in the ilium admitting a thumb. Protruding from this defect was a thin walled hernial sac which spread to a bulge of 3 1/2 inches in diameter. The sac was covered with a thin skin graft. The hernia bulged on coughing and was easily reducible. Pressure on the hernial sac gave the patient a sensation of desiring to defecate.

A triangular flap 3 inches wide at its tip was outlined along the upper border of the scarred area. Originally it extended almost to the spine but its distal 4 inches had sloughed and were replaced by a skin graft. Another flap was outlined over the lower part of the buttock, based along the periphery of the anus.

X-ray examination of the pelvis showed a comminuted fracture of the left wing of the ilium with loss of substance in the upper portion of the defect. A fracture line extended from the defect down to just above the superior margin of the acetabulum. The anterior iliac fragment was rotated anteriorly and lifted downward. Another fracture line extended into the ischioac joint. Radiographic examination after a barium enema demonstrated the herniation of the descending colon (Fig. 2).

The patient wore a canvas corset and by using crutches was able to walk only a few steps. His complaint of instability of his pelvic frame and the sensation that his "insides were falling out."

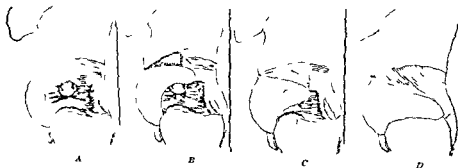


Fig. 3 A, B, C, and D—Diagram depicting successive migration of flap.

The main feature of this case was a large intestinal hernia through a narrow rigid aperture in the iliac wing. This was associated with complete loss of the overlying soft tissues including skin.

The plan for resurfacing was complicated greatly by the loss of a considerable portion of the previously delayed flap. The remaining flap was obviously too small to be shifted directly into the desired position. The skin

over the buttock and the right of the spine was intact and could be adjoined to fill the soft tissue defect but it could not be considered for the resurfacing of the region of the hernia. Therefore it was decided to shift the flap in stages.

Because of the severe eczematoid dermatitis of the grafted areas several weeks elapsed before the patient was ready for surgery. On April 3, 1947, the flap was dissected. The inferior incision along the junction with the scarred area was extended down to the anterior iliac spine. The superior incision was prolonged to the anterior axillary line. The triangular flap was then advanced posteriorly and inferiorly without applying any tension. Posteriorly it was moved about $1\frac{1}{2}$ inches toward the spine. Inferiorly it covered a strip of scarred area about 2 inches wide. The portion of the ear was excised, dissecting it superficially from the hernial sac. The flap was then sutured in its new position joining it to the surrounding skin grafts. The secondary defect above was closed by approximating the superior and posterior borders. The kink set along the posterior border did not interfere with closure since it was adherent to the thick pad of soft tissues from which it was not separated (Fig 3 A and B).

The healing was uneventful. The patient was placed on an extended fasting diet and the patient lost fifteen pounds.

With the flap alongside the hernial aperture and the vitality of the flap assured after repeated dissection it was possible to combine the next stage of resurfacing with the repair of the hernia.



Fig 4—Photograph taken during the second stage showing the flap displaced. Hernial sac was freed and ready to be pulled in side pelvis. The cecum and appendix were not yet removed completely.

On Oct 10, 1947, the upper flap was dissected again and fully mobilized. The scar and skin graft was stripped from the iliac and acral bones and dissected superficially from the hernial sac. A V shaped defect was exposed in the posterior iliac crest measuring 2 by $1\frac{1}{2}$ by 4 inches. The fibrous cover was dissected from the hernial sac freeing it completely (Fig 4). The herniated bowel was readily pushed in side without opening the peritoneal cavity. The internal layer of peritoneum was freed for some distance around the defect. The iliopectineus was laid along the posteromedial aspect. It was used to

obliterate the gap from the inside by pulling it laterally across the defect and securing it to the peritoneum with interrupted sutures of 00 silk. The depression where the bone was missing was filled with a flap of muscle and subcutaneous tissue, most of it fibrotic. The flap was taken from the groin region and was based anterolaterally. The lower border of the external oblique muscle was then sutured over it thereby buttressing the defect from the external surface (Fig 5). The skin flap was brought down over the repaired region with interrupted sutures of cotton No 40.

The skin over the buttock and over the right side of the back was undermined and mobilized. The two skin edges were advanced along a Y suturing them to each other in the form of a Y until they reached the upper skin flap in its new position. The final closure was done with cotton No 40 subcutaneously and silk on the skin surface. An effort was made to bring the skin flaps down to the underlying bare bone using a few cotton sutures tacked down to some fibrous remnant on the bone. The secondary defect resulting from rotation of the flap was covered with a dermatome graft (Fig 3 C). Pressure dressing was applied over the entire operative area reinforced by a bivalved spica.

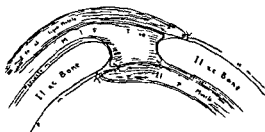


Fig. —Diagram depicting obliteration of iliac defect

Following this operation a sinus developed underneath the scar where the flaps failed to adhere to the underlying bone. Draining of this sinus and application of external pressure failed to obliterate it. It was therefore unroofed by incising the scar. The flaps were allowed to retract and the fibrous walls of the sinus were excised. On November 29 split grafts were applied to the exposed iliac and sacral bone. The take was poor and one month later an additional graft was done. It was not until the middle of February that the wound was epithelialized completely and the patient sent out on furlough.

The partial failure of this operation was attributed to the fact that the skin flaps were sutured under slight tension and inadequate provision was made to keep them in close approximation with the underlying base. As a result there was tenting of the flaps and creation of dead space underneath them which in turn led to sinus formation. Since the floor of the sinus consisted of poorly vascularized sclerotic bone and the scar between the flaps formed the roof there was little tendency to form granulation tissue which would obliterate the sinus spontaneously.

It was felt that the second attempt to join the flaps should be performed in a clean field after a few months interval to allow the flaps to recover. Therefore a temporary resurfacing with thin split grafts was undertaken although it was found very difficult and time consuming to make the temporary graft take on such a poor base.

The hernia was eliminated and the defect in the bone wall buttressed (Fig 6). However the lower iliac region and part of the sacrum were covered with a thin split graft adherent to the bone. These grafts were consid-

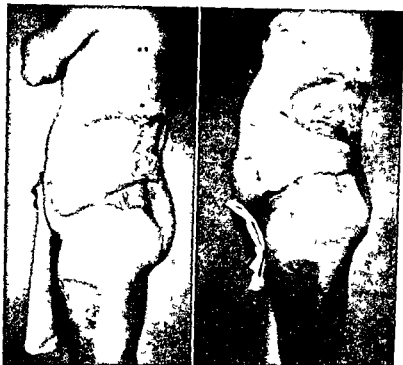


Fig 6

Fig 7

Fig 6—After second stage hernia eliminated flap covers entire region of hernia repair (Courtesy of Army Institute of Pathology)

Fig 7—Final condition



Fig 8—X ray view of pelvis two years after surgery bony defect was obliterated by soft tissue (Courtesy of Dr Samuel Littman)

ered unstable. The iliac and lateral regions, lacking soft tissue padding, were sensitive to pressure. This contributed in large measure to the patient's feeling of instability of his pelvic frame.

On April 4, 1946, the patient was operated upon again. The split grafts were stripped from the bone. The skin flap was dissected again and fully mobilized. It was advanced inferiorly and posteriorly until it lay without any tension alongside the gluteal prominence reaching the posterior skin border. The flap was not stretched by sutures above and below, but was allowed to contract, filling the irregularities of the bony contour. A dermatome graft covered the secondary defect above the flap (Fig. 3 D). The closure was done with subcutaneous cotton sutures and silk on the skin surface. The healing was uneventful. The patient was fitted with a reinforced canvas belt and was referred for physical rehabilitation. His complaints were that the pelvis felt unsteady while he walked and that he tired easily both attributable to the iliac fractures. In August 1946, he was discharged (Fig. 7).

The patient was examined again in June 1949, two years after discharge. He had discarded the canvas belt, was able to walk without a limp for considerable distance, and could perform light physical work. Bowel function was normal. The defect in the bone could not be palpated but was visualized readily by x-rays (Fig. 8).

SUMMARY

A case of a posterior intestinal hernia with extensive destruction of the surrounding soft tissue is described. The following features in the handling of this case deserve emphasis:

1. A large bony defect in the wing of the iliac bone was obliterated without recourse to foreign material, utilizing the surrounding soft tissue inside and outside the pelvis. The iliopsoas muscle was made to form the internal dynamic blockade, while the external oblique muscle was utilized for an outer dynamic liver. The intervening space was obliterated with static tissues which also re-enforced the closure. A firm stable repair was accomplished and no recurrence could be noted when last examined two and one-half years after herniorrhaphy.

2. Extensive resurfacing of this area was coincidentally effected with a well padded contiguous flap. Since the only available contiguous flap was inadequate in size, it was rotated into the desired position in three stages. The repeated dissection of the flap (debriding) assured its vitality and made it possible, with each consecutive stage, to advance the flap further.

3. An attempt to suture the skin flap, even under the slightest tension over an irregular base of sclerotic bone, led to nonadherence of the flap and formation of a subcutaneous sinus. Fusion of the tract, temporary skin grafting, and finally further advancement of the flap were necessary to complete an adequate resurfacing.

REFERENCES

1. Wat on, L. F. *Hernia*. St. Louis, 1918. The C. V. Mosby Company.
2. Gray, Henry. *Anatomy of the Human Body*. Ed. 2^o. Philadelphia, 1930. Lea & Febiger.
3. Treves. Cited by Gray 2.
4. Oliffell, M. C. Iliac Hernia After Bone Cracking. *Lancet* 1: 110, 1945.



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Fig 6—After second stage, hernia eliminated. flap covers entire region of hernia repair (Courtesy of Army Institute of Pathology)

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REFERENCES

1. Watson, L. F. *Hernia*. St. Louis, 1948. The C. V. Mosby Company.
2. Gray, Henry. *Anatomy of the Human Body*. Ed. 22. Philadelphia, 1930. Lea & Febiger.
3. Treves. Cited by Gray.
4. Ollfeld, M. C. Iliac Hernia After Bone Grafting. *Lancet* 1: 110, 1941.

THE HENRY APPROACH TO FEMORAL HERNIA

REPORT OF TWO CASES

JAMES F. MISCROFF M.D.* AND FREDERICK J. MCCREADY M.D.†
ROCHESTER, MINN.

THE Henry approach is an unusual one—it is rarely described in surgical textbooks and infrequently used by surgeons but it does offer many advantages in facilitating repair of a femoral hernia. Therefore we wish to describe the extraperitoneal approach to femoral hernia as suggested by Henry and to report the cases of two patients seen at the Mayo Clinic in which this technique was satisfactorily employed.

The extraperitoneal approach to femoral hernia was first described by Henry¹ in 1936. He recognized the excellent possibilities of this approach for the first time when in performing the operations for bilateral lesions of the lower portion of the urinary tract by means of the midline extraperitoneal approach he noticed the remarkable anatomic exposure it presented of the femoral region. He himself said: "In a thin patient as soon as my hand had displaced the peritoneum from beside the bladder the view obtained of the four relevant structures (Gimbernat's ligament, the hinder edge of Poupart's, the fascia covering the pectineus and the external iliac vein) was like that in a specimen prepared for a demonstration."

Fig. 1 demonstrates the view of the femoral hernia and its related anatomic structures obtained by means of Henry's extraperitoneal approach. First of all optimal exposure is obtained by placing the patient in a modified Trendelenburg position. A low midline incision is made and after the recti muscles are separated the unopened peritoneum is reflected from the lateral pelvic wall by blunt gauze dissection. The hernial sac, Gimbernat's ligament, Poupart's ligament, Cooper's ligament, the pectineal fascia and the external iliac vein are easily identified. In most cases of incarcerated femoral hernia Gimbernat's ligament must be incised in order to relieve the constriction about the neck of the sac. The exposure provided by means of the extraperitoneal approach makes it possible to do this easily without fear of injuring an anomalous obturator artery in the event one is present.

The femoral canal is easily repaired with the ligamentous structures and neighboring vessels in clear view. Poupart's ligament is brought down and sutured to Cooper's ligament as far laterally as the external iliac vein. If there is too much tension on the sutures a small fascial flap can be raised from the pectineal fascia and coapted to Poupart's ligament. As a rule this procedure is not necessary.

REPORT OF CASES

CASE 1—A woman 47 years of age was admitted to the hospital on March 1948. Her condition was acute. She complained of severe abdominal pain and vomiting of three

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hours duration Six years prior to admission after a normal delivery she had noted swellings in both groins The swelling on the left side had disappeared, the one on the right persisted but could be reduced easily by the patient

About three hours before admission the patient experienced a sudden onset of generalized abdominal pain with vomiting The mass in the right groin had become somewhat larger than usual and it was fairly tender and irreducible She had passed gas and feces two hours before admission

On examination the patient appeared to be in good general physical condition Blood pressure was 134 mm. of mercury systolic and 80 mm. diastolic The pulse rate was 90 beats per minute and the temperature was normal The abdomen was soft, flat and non-tender The peristaltic activity appeared normal There was a firm tender mass the size of an egg in the right femoral region Reduction of the mass was not attempted Further examination also revealed a small easily reducible femoral hernia on the left side Laboratory tests were within the normal range

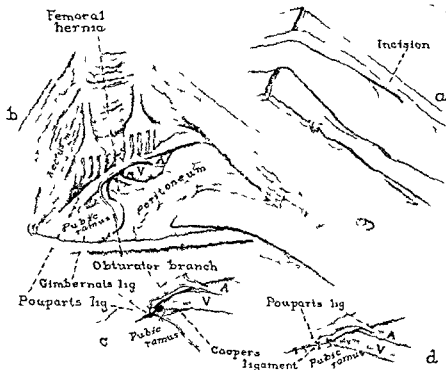


FIG. 1.—View of femoral hernia and its related anatomic structures obtained by means of the extraperitoneal approach of Henry

A diagnosis of incarcerated femoral hernia on the right side and femoral hernia on the left was made and the patient was prepared for operation In view of the presence of bilateral femoral hernia and the good condition of the patient it was decided to use the extraperitoneal approach of Henry and to repair both hernias at the same time through one incision

With the patient under spinal anesthesia and in a modified Trendelenburg position a low midline incision was made The recti were separated and the unopened peritoneum was reflected from the lateral pelvic wall on each side by blunt gauze dissection The extraperitoneal exposure of the right and left hernial sacs and the entrance of each into its

respective femoral canal was excellent. On the right side the neck of the sac which had been incarcerated was released by incising Gimbernat's ligament. The sac was opened and the content proved to be viable omentum which was readily replaced in the peritoneal cavity. The neck of the sac was ligated and the excess was excised. The sac of the femoral hernia on the left side was disposed of in a similar manner. The femoral canal on each side was then obliterated by coapting Poupert's ligament to Cooper's ligament as far laterally as the external iliac vein with nonabsorbable sutures.

The postoperative course was uneventful and the patient was dismissed from the hospital on the ninth postoperative day.

CASE 2—A woman 39 years of age came to the clinic in July, 1948 because of a recurrent femoral hernia on the left side of three months duration. One year previous she had had an abdominal hysterectomy for fibroids and a repair of the femoral hernia elsewhere. Results of physical examination were essentially negative except for a swelling the size of a walnut in the left femoral region and thrombosed external hemorrhoids.

Because of a history of rectal bleeding and the presence of external hemorrhoids, proctologic examination was performed the next morning. External hemorrhoids and an acute angulation of the sigmoid were the only abnormalities noted in the rectum and colon. The procedure was moderately painful for the patient.

Two hours later the patient began to experience diffuse abdominal pain of moderate severity which was aggravated by deep respiration. Examination of the abdomen revealed marked tenderness and rebound tenderness across the entire lower portion of the abdomen although the abdomen remained soft. The recurrent femoral hernia was easily reduced. The temperature was 99.8. The pulse rate was 80 and respirations were 20.

The patient was observed for a few hours but in view of the fact that the abdominal pain and tenderness persisted, she was admitted to the hospital. A surgical consultation was held and because the possibility of perforation of the bowel could not be excluded it was decided to perform an exploration.

Abdominal exploration revealed a considerable amount of thick chocolate-colored fluid in the pelvic cul-de-sac. This was cleaned out and further exploration revealed a ruptured chocolate-colored cyst of the left ovary which had probably been the size of a tangerine. The lower portion of the sigmoid and the recto sigmoid were firmly adherent in the region of the cyst. In view of the patient's age the previous hysterectomy, and the widespread endometriosis all ovarian tissue was removed.

The recurrent left femoral hernia was repaired at the same time. The extraperitoneal approach of Henry was used and this was accomplished through the same incision. The parietal peritoneum was reflected from the left portion of the pelvic wall by blunt gauze dissection and the left femoral region was exposed. There was a small opening one quarter inch in diameter lateral to Gimbernat's ligament in which there was a small hernial sac. The sac was reduced and obliterated and repair of the femoral canal was completed as described in the previous case. Exposure of the right femoral region revealed a moderately enlarged femoral canal. This was closed at the same time.

An uneventful postoperative course ensued.

SUMMARY

In the past there have been essentially two approaches to femoral hernia, namely the inferior or femoral approach and the superior or inguinal approach or some combination of these two. Henry's technique may be considered the third method of approach to femoral hernia. The following are some of the advantages offered by his extraperitoneal midline exposure of the femoral canals.

1. It has been estimated that approximately 20 per cent of femoral hernias are bilateral.² In such cases the hernias can be repaired by this technique.

through one incision. When a single femoral hernia is known to exist and this approach is used, it is possible to visualize the opposite femoral canal with ease and thus determine whether or not the defect is bilateral.

2. An abnormal obturator artery may be ligated under excellent exposure. This artery is present in 20 per cent³ to 30 per cent⁴ of the cases and is a real hazard particularly in carrying out a femoral type of reduction and repair.

3. If ligation of the neck of the sac is carried out at its origin, a peritoneal dimple is not formed as a starting point of a recurrent hernia.

4. The contents of a strangulated femoral hernia are readily dealt with through this approach.

5. A femoral hernia may be repaired coincidentally with necessary surgical measures in the lower portion of the abdomen.

6. The Henry technique furnishes excellent exposure of anatomic structures adjacent to the femoral canal.

In an obese individual we would not advise that this technique of repair of femoral hernia be used routinely because the thick anterior abdominal wall makes exposure difficult. However, one of us (J. E. M.) recently combined the femoral and the midline approaches in repairing a large incarcerated femoral hernia on the right side of a man who weighed 240 pounds. Each approach complemented the other in this difficult operation.

REFERENCES

1. Henry, A. K. Operation for Femoral Hernia by a Midline Extraperitoneal Approach. With a Preliminary Note on the Use of This Route for Reducible Inguinal Hernia. *Lancet* 1: 531-573, 1936.
2. Coley, B. I. Femoral Hernia. In Christopher Freeman, *A Textbook of Surgery*, ed. 1. Philadelphia, 1936. W. B. Saunders Company, pp. 137, 138.
3. Beecher, Lewis, and Johnston, T. B. *Manual of Surgical Anatomy* (revised by John Bruce and Robert Walmsley), ed. 5. London, 1933. Oxford University Press, p. 30.
4. McGregor, A. L. *A Synopsis of Surgical Anatomy*, ed. 3. Baltimore, 1943. William Wood & Company, p. 55.

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REFERENCES

1. Henry, A. K. Operation for Femoral Hernia by a Midline Extraperitoneal Approach, With a Preliminary Note on the Use of This Route for Reducible Inguinal Hernia, *Lancet* 1: 531-533, 1926.
2. Cohn, B. L. Femoral Hernia in Christopher Frederick: A Textbook of Surgery, ed. 1, Philadelphia, 1936, W. B. Saunders Company, pp. 137-1387.
3. Beeley, Lewis, and Johnston, T. B. Manual of Surgical Anatomy (revised by John Bruce and Robert Wainley) ed. 5, London, 1930, Oxford University Press, p. 530.
4. McGregor, A. L. A Synopsis of Surgical Anatomy, ed. 5, Baltimore, 1941, William Wood & Company, p. 82.

RESECTION OF SEGMENTS OF AURICULAR WALL

AN EXPERIMENTAL STUDY

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(From the Memorial Hospital Center for Cancer and Allied Diseases)

CONSIDERABLE interest has now developed in the surgery of vascular anomalies involving the great vessels near the heart patent foramen ovale, acquired valvular disease of the heart, revascularization of the ventricular walls etc. The surgery of cardiac tumors, however has received scant attention and this is readily understood because of the rarity of these growths. Becl¹ cited an instance of successful resection of a localized tumorous mass on the left ventricular wall with relief of symptoms. Intracardiac neoplasms would of course present more technical difficulties. In a recent monograph entitled *The Tumors and Polyps of the Heart*, Mahaim of Lausanne apparently has reviewed all the literature on the subject including pathologic anatomy, physiology, and clinical diagnosis of all types of cardiac neoplasms. The ninth chapter of this work is essentially a theoretical discussion of the possibilities of surgical excision of cardiac neoplasms, the author strikes a somewhat optimistic note stating that if surgeons can remove emboli from the great vessels near the heart, it should not be a far step to excise an intracardiac papilloma especially if the base is narrow and well circumscribed. On a recent occasion the problem of excision of an intra auricular and presumably pedunculated papilloma producing a ball valve action to temporary valvular obstruction was posed to one of us (A B) by Professor A Vannotti of Lausanne such a diagnosis having been made clinically by him in a middle aged male patient. The operation was never attempted the patient since has died in a remote locality and necropsy was not obtained.

With no experience on our part in the technical problems of the surgery of the auricular wall in man, the experiments recorded below suggested themselves.

EXPERIMENTS ON PUPPITS

Manipulation of the heart

PB 1—Weight 8 pound fourteen ounces Chloroform anesthesia. No aseptic technique. Left chest opened by incision along lower left sternal margin. Pericardial sac incised to expose heart.

(a) Ventricles markedly compressed between fingers for 10 seconds. Slight dilatation of ventricles but no mention of normal beat.

(b)

(c)

chambers

PB 2—Weight 7 pound 8 ounces Ether anesthesia. No aseptic technique. Left chest opened as in *PB 1*.

Several rapid compressions of the entire heart were carried out and all chambers dilated markedly with death of the animal.

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PB 3—Weight 11 pounds Ether anesthesia No aseptic technique Left chest opened as in PB 1 and PB 2 Heart exposed

Auricles compressed with fingers for 15 seconds on two occasions Return of normal beat but then rapid dilatation of all chambers After second compression dilatation did not increase but heart became arrested and rabbit died Opening and closure of isolated portion of left auricle

EB 4—Weight 10 pound 8 ounces Ether anesthesia No aseptic technique Left chest entered as in previous experiment Heart exposed A rubber hood small curved hemostat was placed transversely across base of left auricular appendage The isolated portion of the latter was opened, interior examined and the opening then closed with a continuous stitch of 00 silk on a curved atraumatic needle The clamp was removed and isolated portion of auricle again filled with blood Heartbeat apparently normal Seven weeks later the animal was alive and active (Fig 1)

Ligature isolation of auricular appendage with excision of isolated segment (Figs 2 and 3)



FIG 1—Diagrammatic illustration of experiment PB 4 A Rubber hood small curved hemostat applied to base of auricular appendage The latter has been slit and interior examined B Incision has been repaired by continuous suture and clamp removed Normal heartbeat Animal survived

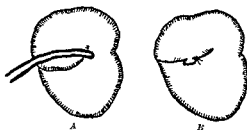


FIG 2—Diagrammatic illustrations of experiments PB 1 and those following A Clamp placed across base of auricular appendage B Ligature applied beneath clamp and latter removed Portion of auricular appendage distal to clamp cut away

PB 1A and PB 2A—In these animals the left side of the chest was opened under ether anesthesia No aseptic technique A silk ligature was placed about the base of the left auricular appendages beneath a curved hemostat which was applied transversely across their bases The ligature was tied thus closing the appendage and the portion of the auricular wall distal to the ligature was cut away (Fig 3) The measurements were 5 to 10 mm in length The hearts apparently continued to beat normally The animals died in twenty-six and forty-eight hours respectively Necropsy revealed widespread mediastinitis (Aseptic technique had not been employed during operations)

PB 1B PB 2B and EB 3B—Experiments as before One animal died during the experiment (anesthesia) and in the second the auricle was traumatically ruptured with death from hemorrhage The third animal survived and was normal during an observation period of several weeks

PB 1C EB 2C PB 4C JB 4C and GJ —Experiment as before. No anesthetic technique. Two animals survived and were well ten days after operation. Two died during the operation of bilateral pneumothorax and accidental severance of a pulmonary artery, respectively. One survived six weeks and died of left emphysema.

EXPERIMENTS ON DOGS

Dogs of both sexes were anesthetized with nembutal and ether (positive pressure). With regular aseptic procedure a linear incision was made along the left margin of the sternum to enter the chest cavity and expose the pericardial sac. The anterior surface of the latter was grasped with two hemostats and between them a small incision made which was enlarged to exposure of the anterior aspect of the heart.



Fig. 3—Photograph of formalin hardened segments of auricles and auricular appendages excised in experiments on rabbits (See text).



Fig. 4—Photograph of hearts from Dogs 11 and 19. Animal was sacrificed six weeks after one auricular appendage was excised as shown in Fig. 4I and 4I' intact auricular appendages II and II' sites of healed wounds resulting from excision of auricular appendages.

The margin of the tip of the right auricle was grasped with a large curved hemostat and the whole auricle pulled upward. Another curved hemostat was applied to the base of the auricle transversely and that portion of the auricle above the clamp cut away. A ligature was applied beneath the clamp and tied. The pericardial sac was then closed (Fig. 4).

Following the operation the heart exhibited no appreciable change nor showed even a slight general dilatation.

More details of the protocols are summarized as follows:

Dog 11—Convalescence uneventful. Dog died of 19 weeks after operation with no apparent abnormality.

Dog 12—Recovery from operation satisfactory. On sixth day chest wound appeared infected and bleed. On the ninth postoperative day the animal appeared very ill and was sacrificed. Necropsy revealed bilateral lobar pneumonia and infected wound in chest wall. Wound in heart healed and clean.

Dog 13—Convalescence uneventful. Dog died of 109 weeks after operation. No abnormality at this time.

Dog 14—Upon incision of pericardium there seemed to be dense adhesions obliterating the pericardial cavity. When these were being separated a large rent was produced in the auricle with excessive hemorrhage and collapse of the animal and death.

Dog 15—Convalescence uneventful. Dog died of 19 weeks after operation. No abnormality.

Dog 21—Convalescence uneventful. Dog died of 66 weeks after operation. No abnormality.

DISCUSSION

Portions of the ventricular wall were successfully excised in the dog by Murray³ after preliminary vascular occlusion. As mentioned previously, Beck successfully removed a tumorous mass from the ventricular wall of a human patient.

In the rabbit experiments just summarized it was shown that marked compression of the heart for periods of 15 to 20 seconds was followed by dilatation of all chambers and when the compression was repeated by death. One experiment demonstrated that a portion of the auricle could be temporarily isolated by compression and opened and closed by suture without apparent permanent disturbances. A third series of experiments illustrated the feasibility of excision of part of the auricular appendage distal to a clamp with repair of the clamped segment. Similar experiments on a series of dogs carried out with aseptic technique also showed the feasibility of removal of a large segment of auricular appendage without interruption of normal heart action and with prolonged survival of the animals.

REFERENCES

1. Beck, Charles C. Section on Surgery of the Heart and Pericardium in Christopher & Textbook of Surgery Philadelphia 1942. W. B. Saunders Company p. 1007.
2. Mahaim, Ivan. Les tumeurs et les polypes du coeur. Paris, 1915. Masson & Cie.
3. Murray, Gordon. The Pathophysiology of the Cause of Death From Coronary Thrombosis. Ann. Surg. 128, 3-3, 1947.

DELAYED PRIMARY CLOSURE OF CONTAMINATED WOUNDS

A REPORT BASED ON FORTY SIX CASES

JOSEPH H. MORRIS, M.D., AND GEORGE H. MARTIN, M.D. VICKSBURG, MISS.

(From the Surgical Section of The Street Clinic and Mercy Hospital)

IN SPITE of recent advances made in the management of wounds of all types there remains a high incidence of postoperative infections in grossly contaminated wounds. Primary closure of surgical incisions is usually followed by uninterrupted healing but wounds contaminated by frank pus or by the contents of the lower gastrointestinal tract, especially the colon, often become infected if closed primarily.

Secondary closure is the term applied to the technique of the delayed closing of a wound by revision and suture, that is by mobilizing the retracted skin margins and excising the granulation tissue in the base of the wound. Delayed primary closure may be defined as the technique of closing surgical incisions or accidental wounds previously prepared, after a period of delay but without revision being necessary. A delayed primary closure may be done from twenty-four hours following the original preparation of the wound until five or six days later.¹ After six days the skin margin will begin to retract inward and granulation tissue will appear in the wound making secondary closure necessary.

Primary closure of previously debrided wounds after a period of delay was first used by French surgeons during World War I.² Their technique consisted of primary debridement, flapping pack, and closure in six days. A culture was taken twenty-four hours after the primary debridement and if hemolytic streptococci were found the wound was left open. The advantages of this procedure were (1) the practical elimination of gas bacillus infection and (2) marked diminution in the number of pyogenic infections. The disadvantages were the possibility of secondary contamination of an open wound and the necessity of two operations instead of one. The advantages far outweighed the risk of infection incurred in primary suture of doubtful wounds.³

This technique of delayed primary closure was revived by Collier for the management of grossly contaminated operative incisions especially those contaminated by the contents of the lower gastrointestinal tract. Where primary closure was done he reported an incidence of 50 per cent infection in wounds contaminated by the contents of the lower bowel. This was true in spite of the fact that it was customary to use a drain. In Collier's series delayed primary closure was done in twenty-one cases. There was uninterrupted healing in all patients except one who developed a trivial infection.⁴

The same organisms may be grown at the time of completion of a delayed closure that were present originally in these grossly contaminated wounds. This suggests that the technique does not have a bactericidal or bacteriostatic effect but in some way prepares the wound so that it is more resistant to invasion by

the organisms present.¹ Even when infection occurs it tends to remain localized to the surface of the wound without the production of a spreading cellulitis.² It has been shown by duMortier that incisions in the abdominal wall of guinea pigs contaminated with *Staphylococcus aureus hemolyticus* have little resistance to bacterial invasion during the first six hours. After the wounds had been closed twelve hours and the bacteria applied there was infection but it usually remained localized. From this time onward the percentage of severe infection steadily decreased for the next five days after which time it was no longer possible to infect these wounds by swabbing organisms on the surface.^{10, 11}

There is a minimum of devitalized tissue in surgical incisions but in spite of adequate hemostasis and wound coaptation there remains a variable amount of blood clot and serum in the wound especially in the fatty subcutaneous tissue. This blood clot and serum provide a medium for growth of all types of aerobic bacteria. Devitalized tissue although small in amount provides favorable circumstances for the growth of anaerobic organisms.⁶ It has long been known that granulation tissue is more resistant to all types of organisms than are unprotected raw wound surfaces. Thus by primary delayed closure one removes the majority of wound pabulum and provides the wound surfaces with a protective coating of fibrin, leucocytes and beginning capillary buds.

The wounds selected for delayed primary closure in this series were grossly contaminated either with pus or with contents of the gastrointestinal tract. If closed primarily one would expect a high incidence of serious wound infection with such contamination.

The technique used by us is similar to that described by Coller (Fig. 1). The peritoneum and fascia are closed with interrupted cotton sutures. Vertical mattress sutures of single filament nylon are then placed deeply through the fat and skin so that alternate sutures can be tied on opposite sides of the wound. This prevents tangling of the ends of the sutures which are left long to be tightened later. Two small packs are introduced from opposite ends of the incision, beneath the sutures meeting in the center of the wound. The sutures are tied loosely with a double twist single knot care being taken not to approximate the skin edges. Arbitrarily forty eight hours is selected as the period of delay before removing the pack and completing the closure.⁴ This is done at the patient's bedside using only mild sedation.^{4, 5}

At first fine mesh gauze was used for the pack but this later was replaced with rayon gauze 114 by 114 mesh as described by Owens.¹² This material was chosen because it can be removed with less trauma to the wound margins. Its coefficient of friction is low and the mesh is fine enough to prevent ingrowth of capillary buds but coarse enough to allow for the absorption of serum and blood.¹² The rayon gauze pack was saturated with penicillin, gentamicin and streptomycin or normal saline solution.^{7, 8} A drain was left in the abdominal cavity in some cases and beneath the anterior rectus sheath in others. In all the cases in which drains were used the drains were brought out through the wound.

From Table I it may be seen that in this series of forty six consecutive contaminated wounds there were fourteen infections. Six of these were trivial

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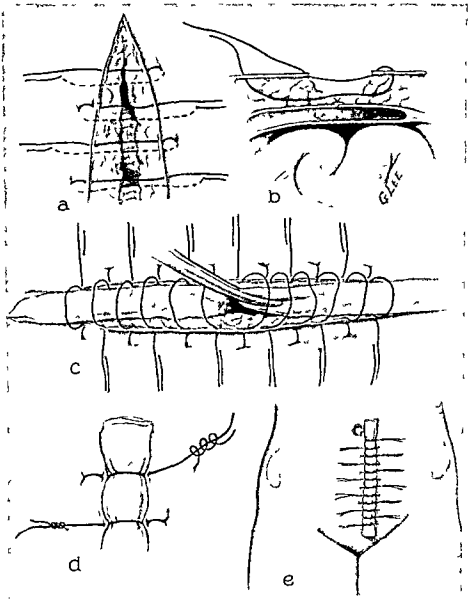
NO	NAME	PATHOSIS	OPERATION	HEALING	DAYS INFLATED
1	F J	Ventral hernia cellulitis of skin	Fascial overlap	Trivial infection	None
2	L H	Intestinal obstruction perforation of ileum	Drainage of abscess freeing of adhesion	No infection	None
3	J J	Umbilical hernia erosion of skin over hernial sac	Mayo hernioplasty repair of intestine	No infection	None
4	P Y	Strangulated hernia, gangrene of ileum	Re section of ileum	No infection	None
5	R S	Postoperative strangulated hernia	Fascial overlap	No infection	None
6	H B	Obstructing duodenal ulcer	Partial gastrectomy	No infection	None
7	G W	Perforated duodenal ulcer generalized peritonitis	Gastrostomy	No infection	None
8	A H	Obstructing duodenal ulcer	Partial gastrectomy	No infection	None
9	T M	Carcinoma of sigmoid colon	Obstructive resection	No infection	None
10	T W	Carcinoma of sigmoid colon	Closure of colostomy	Trivial infection	None
11	L C	Carcinoma of rectum with obstruction	Second stage colostomy resection	No infection	None
12	J N	Carcinoma of sigmoid colon	Closure of colostomy	No infection	None
13	T C	Acute appendicitis with perforation	Appendectomy drain beneath fascia	No infection	None
14	G P	Perforated appendix with appendiceal abscess	Appendectomy and drainage of abscess	Serious infection	0
15	O S	Acute appendicitis with perforation	Appendectomy	Serious infection	7
16	L T	Obstructing duodenal ulcer	Partial gastrectomy	No infection	None
17	L I	Acute appendicitis with perforation	Appendectomy	No infection	None
18	H B	Acute appendicitis with perforation	Appendectomy	No infection	None
19	A R			Trivial infection	4
20	R S			Serious infection	2-
21	R K	Obstructing duodenal ulcer	Partial gastrectomy	No infection	None
22	J T	Obstructing duodenal ulcer	Partial gastrectomy	No infection	None
23	M S	Obstructing duodenal ulcer	Partial gastrectomy	No infection	None
24	W B	Carcinoma of sigmoid colon	Primary resection	No infection	None
25	W B	Carcinoma of sigmoid colon	Closure of colostomy	No infection	None
26	R R	Diverticulitis of sigmoid colon with perforation	Obstructive resection	Trivial infection	7
27	P S	Obstructing duodenal ulcer	Partial gastrectomy	Trivial infection	None
28	J M	Stab wound of abdomen with perforation of ileum	Repair of perforation drain beneath fascia	Serious infection	7

TABLE I—CONT'D

NO	NAME	DYCNOSIS	OPERATION	HEALING	DAYS DELAYED
1	E M	Sarcoma of sigmoid and ileum	Obstructive resection	No infection	None
0	F M	Sarcoma of sigmoid and ileum	Closure of colostomy	Trivial infection	4
31	J W	Intussusception gran- ule of ileum and cecum	Closure of colostomy	No infection	None
3	P T	Gun shot wound of the abdomen perforation of rectum and ileum	Repair of perforation colostomy	No infection	None
33	R T	Gun shot wound of the abdomen perforation of rectum and ileum	Closure of colostomy	No infection	None
34	H B	Perforated appendix generalized peritonitis	Appendectomy peri- toneal drain	Serious infection	14
23	B R	Perforated appendix	Appendectomy	No infection	None
36	L D	Strangulated ventral hernia	Mayo hernioplasty	No infection	None
37	W T	Obstrucing duodenal ulcer	Partial gastrectomy	No infection	None
38	A W	Carcinoma head of pancreas	Cholecystojejunostomy	No infection	None
39	C S	Carcinoma of sigmoid colon	Closure of colostomy	No infection	None
40	E M	Obstructing duodenal ulcer	Partial gastrectomy	No infection	None
41	H H	Ovarian cyst perfora- tion of sigmoid	Repair of perfora- tion peritoneal drain	Serious infection	11
42	H H	Fecal fistula	Excision of fistula repair of sigmoid	No infection	None
43	W N	Perforated appendix	Appendectomy	No infection	None
44	H B	Carcinoma of stomach	Partial gastrectomy	No infection	None
45	A A	Perforated duodenal ulcer	Gastrostomy drain beneath fascia	Serious infection	14
46	W P	Gunshot wound of ab- domen perforation of sigmoid and ileum	Repair of perforation drain beneath the fascia	Serious infection	8

there being a serous discharge but no delay in wound healing. There were eight serious infections with a delay of from seven to twenty-two days in wound healing. However in four of these intra-abdominal drains were brought out through the wound and the continued drainage of purulent material from the peritoneal cavity contributed to the wound infection. In three of these serious infections drains were left beneath the fascia and brought out through the wound. In nearly every case in which a drain was brought out through the wound an infection occurred. In only one case was there a serious infection in which a drain was not used.

Drains should be used infrequently but when it is deemed necessary to leave a drain within a localized intraperitoneal abscess it should be brought out through a separate stab wound to prevent continued contamination of the incision. If a drain must be left beneath the anterior rectus sheath, it too may be brought out through a separate stab wound. However it would seem that the occasion for leaving a drain beneath the anterior rectus sheath should be infrequent since the resistance of this tissue to infection is high as compared to the fat and subcutaneous tissue.



1. Testis and fascia closed
Payon gauze
with single
brought out

The incidence of infection both serious and trivial in this series of cases is 30.4 per cent. Eight or 17.4 per cent were serious infections with the majority occurring in wounds in which drains were used.

It is not possible from this study to determine the value of penicillin and streptomycin locally, but it would seem that these two antibiotics in aqueous solution might be of value in conjunction with delayed primary closure.

CONCLUSIONS

- 1 Delayed primary closure will lower the incidence of infection in grossly contaminated surgical incisions.
- 2 Of the infections that occur a high percentage will be trivial without delay in wound healing.
- 3 Drains from within the abdomen or beneath the anterior rectus sheath should be brought out through a separate stab wound.
- 4 Rayon gauze is an ideal pack because there is minimal amount of trauma on removal.
- 5 It would seem that penicillin and streptomycin in aqueous solution have some antibacterial effect and help to prevent subcutaneous infections if used locally in conjunction with a rayon pack.

REFERENCES

- 1 Lemberston J de J and Black, B M. Delayed Closure of Incisions Made at Closure of Colonic Stomas, Surg. Gynec. & Obst. 76: 390 1943.
- 2 Pool E H. War Wounds: Primary and Secondary Suture. J. A. M. A. 73: 383-387, 1919.
- 3 Collier F A and Valk, W L. Delayed Closure of Contaminated Wounds. Preliminary Report. Ann. Surg. 112: 266-270 1940.
- 4 Collier F A and Vaughan H H. Treatment of Carcinoma of Colon. Ann. Surg. 121: 392-411 1945.
- 5 Allen, A W. Symposium on Surgical Management of Malignancy of Colon. Carcinoma of Colon. SURGERY 14: 350-365 1943.
- 6 Lyons C. Philosophy of Wound Management in United States Army, Bull. Am. Coll. Surgeons 30: 15-14 1945.
- 7 Lyons C. Penicillin Therapy of Surgical Infections in the U. S. Army. Report. J. A. M. A. 123: 1007-1014 1947.
- 8 Reinhold L. Delayed Suture of War Wounds. SURGERY 21: 200-207 1947.
- 9 Farris J M and Jones T B. Some Observations on Wound Healing. Clinical Study With Note on Topical Chemotherapy and Secondary Closure. Surg., Gynec. & Obst. 84: 203-212 1947.
- 10 Howes E L, Spoor J W and Harvey S C. Healing of Wounds as Determined by Their Tensile Strength. J. A. M. A. 92: 43-45 1923.
- 11 DuMortier J J. Resistance of Healing Wounds to Infection. Surg., Gynec. & Obst. 56: 762, 66 1933.
- 12 Owens N. Pilon, Ideal Surgical Dressing for Surface Wound. SURGERY 19: 482-483 1946.

STREPTOMYCIN THERAPY IN ESTABLISHED WOUND INFECTIONS

MAJOR EDWIN J. PULASKI AND LIEUTENANT JAMES F. CONNELL, JR.,
MEDICAL CORPS UNITED STATES ARMY

INTRODUCTION

THIS is an analysis of 200 cases of streptomycin treated nontuberculous infections of soft tissues in hospitals of the United States Army. It corroborates and supplements an earlier report.*

RESULTS

The bacterial flora cultured from 172 of the 200 cases are listed in Table I. There were 25 acute infected closed wounds not cultured; these were presumably coecal in origin. *Staphylococcus aureus* was predominant. Two thirds of the lesions had a mixed flora.

Out of 200 cases 135 patients were given streptomycin alone. The remaining 65 were being treated also with penicillin even though penicillin alone had been ineffective.

The results show that 52 per cent of all patients benefited. The response was doubtful in another 11 per cent and negligible in the remaining 37 per cent. Response to therapy was indicated by the pathogenesis of the lesion. The pathogenesis fell into three groups: (1) cellulitis, (2) superficial and deep abscesses, and (3) miscellaneous. Description of the response by the various groups follows.

Group I, Cellulitis (Table II).—Lesions with cellulitis occur over a large area and may suppurate. Of the 52 patients treated 90 per cent benefited with either streptomycin alone or with streptomycin plus penicillin. The 10 per cent listed as doubtful or failures were acute flares in scar tissue. Adjuvant measures were limited to needle aspiration or stab wound drainage. The results thus compared favorably with those obtained with penicillin alone. The usual dose of streptomycin was 2 Gm. daily given in four doses for from four to seven days. Untoward reactions were rare with this dosage.

Group II, Superficial and Deep Abscesses (Tables III and IV).—Lesions of superficial and deep abscesses are grouped together because their response to therapy is similar.

The abscesses in the 51 cases (Table III) occurred in traumatic wounds, the urinary system and as furuncles and carbuncles. Best results took place in infected traumatic wounds where 61 per cent were benefited. Improvement in the urinary tract lesions was only 33 per cent and with furuncles and carbuncles only 20 per cent.

For adequate response the following measures were necessary: (1) free drainage and (2) appropriate excision of dead tissue. Failure with strepto-

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TABLE I BACTERIOLOGY OF 172 CASES OF WOUND SUPPURATION

ORGANISM	TOTAL	PURE		MIXED	
		NUMBER	PER CENT	NUMBER	PER CENT
<i>Staphylococcus aureus</i>	131	34	26	97	74
<i>Streptococcus beta hemolyticus</i>	21	2	10	19	90
<i>Streptococcus nonhemolyticus</i>	34	3	9	31	91
<i>Escherichia coli</i>	39	12	31	27	69
<i>Haemophilus pneumoniae</i> (Friedlander's)	39	8	21	31	79
<i>Proteus vulgaris</i>	41	7	17	34	83
<i>Neisseria meningitidis</i>	17	12	71	5	29
Others	3	3	100	0	0

Twenty eight cases were not cultured

TABLE II GROUP I RESULTS OF THERAPY IN 33 WOUNDS WITH CELLULITIS

DIAGNOSIS	STREPTOMYCIN ALONE				STREPTOMYCIN WITH PENICILLIN			
	NUMBER OF CASES	BENEFITED	DOUBTFUL	NOT BENEFITED	NUMBER OF CASES	BENEFITED	DOUBTFUL	NOT BENEFITED
Cellulitis	18	1	0	1	8	8	0	0
Cellulitis with suppuration	21	17	1	3	6	6	0	0
Total	39	18	1	4	14	14	0	0

TABLE III GROUP II RESULTS OF THERAPY IN 51 SURGICAL ABSCESSSES

DIAGNOSIS	NUMBER OF CASES		BENEFITED		DOUBTFUL		NOT BENEFITED	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
1	3	13	0	0	3	13	0	0
2	4	20	0	0	4	20	0	0
3	1	5	0	0	1	5	0	0
4	5	10	1	20	4	80	0	0

TABLE IV GROUP II RESULTS IN 51 POSTOPERATIVE WOUND INFECTIONS

DIAGNOSIS	NUMBER OF CASES		BENEFITED		DOUBTFUL		NOT BENEFITED	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Abdominal wall	2	10	2	100	0	0	0	0
Flank	10	5	4	40	1	10	5	50
Perineum	6	1	16	100	1	16	4	66
Wound revisions	41	19	43	105	6	14	17	41
Total	59	34	44	75	7	12	26	44

mycin was associated with (1) recurrence of infection in scar (2) dead tissue (3) constant source of reinfection from fistula or sinus and (4) inadequate drainage.

The 51 postoperative wound infections (Table IV) accounted for 40 per cent of our cases. Of these lesions 50 per cent developed under the prophylactic use of penicillin. In 46 cases treatment was by streptomycin alone and in the other 5 a combination of streptomycin and penicillin was used. 42 per cent of the patients were benefited, 23 per cent were doubtfully benefited and 40 per cent were unaffected. The results with either penicillin plus streptomycin or streptomycin alone were similar.

The postoperative infections included 22 of the abdominal wall, 12 of the flank, 6 of the perineum and 41 wound revisions. One half of the nonhealing

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Out of 200 cases 175 patients were given streptomycin alone. The remaining 25 were being treated also with penicillin, even though penicillin alone had been ineffective.

The results show that 52 per cent of all patients benefited. The response was doubtful in another 11 per cent and negligible in the remaining 37 per cent. Response to therapy was indicated by the pathogenesis of the lesion. The pathogenesis fell into three groups: (1) cellulitis, (2) superficial and deep abscesses, and (3) miscellaneous. Description of the response by the various groups follows.

Group I, Cellulitis (Table II).—Lesions with cellulitis occur over a large area and may suppurate. Of the 52 patients treated, 90 per cent benefited with either streptomycin alone or with streptomycin plus penicillin. The 10 per cent listed as doubtful or failures were acute flares in scar tissue. Adjuvant measures were limited to needle aspiration or stab wound drainage. The results thus compared favorably with those obtained with penicillin alone. The usual dose of streptomycin was 2 Gm. daily, given in four doses for from four to seven days. Untoward reactions were rare with this dosage.

Group II, Superficial and Deep Abscesses (Tables III and IV).—Lesions of superficial and deep abscesses are grouped together because their response to therapy is similar.

The abscesses in the 51 cases (Table III) occurred in traumatic wounds, the urinary system, and as furuncles and carbuncles. Best results took place in infected traumatic wounds where 61 per cent were benefited. Improvement in the urinary tract lesions was only 33 per cent and with furuncles and carbuncles only 20 per cent.

For adequate response the following measures were necessary: (1) free drainage, and (2) appropriate excision of dead tissue. Failure with strepto-

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TABLE I BACTERIOLOGY OF 473 CASES OF WOUND PUPLICATION*

ORGANISM	TOTAL	PURE		MIXED	
		NUMBER	PER CENT	NUMBER	PER CENT
<i>Staphylococcus aureus</i>	131	34	26	97	74
<i>Streptococcus beta hemolytic</i>	21	2	10	19	90
<i>Streptococcus nonhemolytic</i>	34	3	9	31	95
<i>Escherichia coli</i>	70	12	17	58	83
<i>Klebsiella pneumoniae</i>	30	5	17	25	83
<i>Streptococcus pyogenes</i>	41	3	7	38	93
<i>Staphylococcus pyogenes</i>	17	2	12	15	88
<i>Others</i>	2	2	100	2	100

Twenty eight closed lesions not cultured

TABLE II (GROUP I) RESULTS OF THERAPY IN 31 WOUNDS WITH CELLULITIS

DIAGNOSIS	NUMBER OF CASES	STREPTOMYCIN ALONE			STREPTOMYCIN WITH PENICILLIN		
		BENEFITED	DOUBTFUL	NOT BENEFITED	BENEFITED	DOUBTFUL	NOT BENEFITED
Cellulitis	18	17	0	1	9	0	0
Cellulitis with suppuration	21	17	1	3	6	0	0
Total	39	34	1	4	15	0	0

TABLE III (GROUP II) RESULTS OF THERAPY IN 31 SURGICAL ABSCESSSES

DIAGNOSIS	NUMBER OF CASES	BENEFITED		DOUBTFUL		NOT BENEFITED	
		NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Fragrant wound	3	3	100	0	0	0	0
Carbon lesions and furuncles	16	3	19	4	25	9	56
Primary abscess	12	0	0	2	17	10	83
Total	31	6	19	6	19	19	61

TABLE IV (GROUP II) RESULTS IN 81 POSTOPERATIVE WOUND INFECTIONS

DIAGNOSIS	NUMBER OF CASES	BENEFITED		DOUBTFUL		NOT BENEFITED	
		NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Abdominal wall	22	10	45	2	9	10	45
Flank	12	0	0	1	8	11	92
Perineum	6	1	17	1	17	4	67
Wound revisions	41	18	44	6	14	17	41
Total	81	31	38	10	12	40	49

infection was associated with (1) recurrence of infection in scar (2) dead tissue (3) constant source of infection from fistula or sinus and (4) inadequate drainage.

The 81 postoperative wound infections (Table IV) accounted for 40 per cent of our cases. Of these lesions 80 per cent developed under the prophylactic use of penicillin. In 46 cases treatment was by streptomycin alone and in the other 35 a combination of streptomycin and penicillin was used. 42 per cent of the patients were benefited, 13 per cent were doubtfully benefited and 45 per cent were unaffected. The results with either penicillin plus streptomycin or streptomycin alone were similar.

The postoperative infections included 22 of the abdominal wall, 12 of the flank, 6 of the perineum and 41 wound revisions. One half of the nonhealing

STREPTOMYCIN THERAPY IN ESTABLISHED WOUND INFECTIONS

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INTRODUCTION

THIS is an analysis of 200 cases of streptomycin treated nontuberculous infections of soft tissues in hospitals of the United States Army. It corroborates and supplements an earlier report.*

RESULTS

The bacterial flora cultured from 172 of the 200 cases are listed in Table I. There were 28 acute infected closed wounds not cultured; these were presumably coccal in origin. *Staphylococcus aureus* was predominant. Two thirds of the lesions had a mixed flora.

Out of 200 cases, 135 patients were given streptomycin alone. The remaining 65 were being treated also with penicillin, even though penicillin alone had been ineffective.

The results show that 52 per cent of all patients benefited. The response was doubtful in another 11 per cent and negligible in the remaining 37 per cent. Response to therapy was indicated by the pathogenesis of the lesion. The pathogenesis fell into three groups: (1) cellulitis, (2) superficial and deep abscesses, and (3) miscellaneous. Description of the response by the various groups follows.

Group 1. Cellulitis (Table II).—Lesions with cellulitis occur over a large area and may suppurate. Of the 52 patients treated, 90 per cent benefited with either streptomycin alone or with streptomycin plus penicillin. The 10 per cent listed as doubtful or failures were acute flares in scar tissue. Adjuvant measures were limited to needle aspiration or stab wound drainage. The results thus compared favorably with those obtained with penicillin alone. The usual dose of 6 to seven grams daily.

Group 2. Abscesses (Table III).—Lesions of superficial and deep abscesses are grouped together because their response to therapy is similar.

The abscesses in the 51 cases (Table III) occurred in traumatic wounds, the urinary system, and as furuncles and carbuncles. Best results took place in infected traumatic wounds where 61 per cent were benefited. Improvement in the urinary tract lesions was only 33 per cent, and with furuncles and carbuncles only 20 per cent.

For adequate response the following measures were necessary: (1) free drainage, and (2) appropriate excision of dead tissue. Failure with strepto-

*—1. Problems, Thirty-Fourth Clinical Conference, O. C. 1943.

7 Topical application of streptomycin was of no value

8 The recommended dosage is 20 to 25 Gm streptomycin q.i.d. for four to eight days. Toxic reactions are uncommon with this dosage

CONCLUSIONS

Streptomycin is of benefit in surgical infections yet it is not a panacea. It is most effective in cellulitis, but only moderately effective in cases of adequately drained superficial and deep abscess. The most beneficial effects of therapy are observed in acute infections when the drug is given early in the disease. Thus, the principal uses of the drug are for gram positive and mixed infections in which there has been no response to maximal doses of penicillin within forty-eight to seventy-two hours or earlier if *in vitro* evidence of penicillin resistance can be secured. In chronic suppurating lesions the drug is useful only as an adjunct to drainage and resection of compromised tissue for the suppression of residual bacteria. In our experience topical application of streptomycin has not given good results.

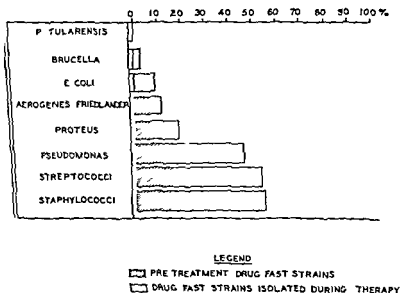


Fig. 1—Streptomycin fastness *in vivo*

Two-thirds of open pyogenic surgical infections are polybacterial. Careful bacteriologic analysis of the wound bacteria and culture sensitivity testing are necessary prerequisites to successful streptomycin therapy. This antibiotic has inhibitory action on most aerobic gram negative and gram positive surgical organisms but wide variation in susceptibility is observed and initially streptomycin fast organisms are found (Fig. 1). Drug fastness is a common factor in unsatisfactory therapeutic responses. For this reason, the drug should be used only when properly indicated. The requisites for successful streptomycin therapy are (1) streptomycin sensitive organisms (2) a dosage of at least 20 Gm a day (3) adequate blood supply and (4) absence of necrotic tissue.

abdominal wounds were complicated by fecal fistulas. The usual daily dose of streptomycin was 2.5 Gm. for from seven to ten days.

Poor results accompanied the following: (1) fecal fistulas, (2) foreign bodies, as bone chips, plastics, silk and cotton or metal, (3) urinary fistulas and (4) sloughing perineal wounds.

Group III, Miscellaneous Wound Infections (Table V)—The miscellaneous infections gave the least response to streptomycin. Thus, unsatisfactory results occurred in cutaneous gangrene, Buerger's disease, chronic tenosynovitis, chronic burns, chronic ulcers and chronic fistulas. In the 4 patients doubtfully benefited, 2 with ecthyma and 2 with decubitus ulcer, streptomycin apparently initiated improvement, but bacteria persisted and wound healing did not occur. The wounds were closed by excision and grafting.

TABLE V. GROUP III. RESULTS OF THERAPY IN 12 MISCELLANEOUS WOUND INFECTIONS TREATED WITH STREPTOMYCIN

DIAGNOSIS	NUMBER OF CASES	BENEFITED	DOUBTFUL	NOT BENEFITED
Ecthyma	2	0	2	0
Decubitus ulcer	2	0	2	0
Chronic burns (second and third degree)	3	0	0	3
Buerger's disease	3	0	0	3
Sinus and fistula	4	0	0	4
Acute tenosynovitis	1	0	0	1
Total	12	0	4	12

One patient treated with streptomycin and penicillin

Topical application of streptomycin as ointments, packs, and irrigations has been ineffective in our hands. Bacteria especially cocci, pyocyanus and proteus in infected sloughing and granulation tissue may become streptomycin fast within one or two days. If bacteria are not eliminated from wounds after two or three applications of streptomycin, further local treatment is useless.

SUMMARY

1. Over all benefit in 200 streptomycin treated nontuberculous infections of soft tissues was 52 per cent.

2. Patients who were treated also with penicillin showed no greater benefit.

3. Of the patients with cellulitis, 90 per cent benefited from streptomycin therapy.

4. Superficial and deep abscesses required adjuvant measures for beneficial response. Of the patients with infected traumatic wounds 61 per cent were benefited. Furuncles and carbuncles improved in only 20 per cent of the cases while infections connected with the urinary tract were suppressed in only 33 per cent of the cases.

5. In postoperative wound infections 42 per cent were benefited. Factors which contributed to poor results are listed.

6. Miscellaneous infections (cutaneous gangrene, Buerger's disease, chronic tenosynovitis, chronic burns, chronic ulcers and chronic fistulas) had least response to streptomycin.

In the five patients of the acute experimental group glomerular filtration rate and maximal tubular reabsorption of phosphate were measured for three consecutive ten minute periods before bacitracin was administered. Then 2000 units of bacitracin were administered intravenously in one to two minutes followed by the administration of 260 units of bacitracin per minute for approximately one hour. During the latter period the same renal function studies were repeated for six consecutive ten minute periods. As effective renal plasma flow and maximal excretion of para-aminohippurate cannot be measured simultaneously, the former renal function was determined in Patients 1, 2, and 3 and the latter in Patients 4 and 5.

In the chronic experiments all of the renal functions described were determined in each of the six patients before and after the intramuscular administration of bacitracin. Patients 1, 2, 3, 4, and 5 received 49,000 to 50,000 units of bacitracin every six hours for four to thirteen days. Patient 6 received three doses of 50,000 units of bacitracin intramuscularly for two consecutive days, none for the next six days, and then four injections of 50,000 units each in the twenty-four hours preceding the final renal function tests. In two patients, 1 and 3, the studies were repeated two and four weeks respectively after the administration of bacitracin had been discontinued. After bacitracin therapy in Patient 5 the total renal plasma flow was also measured according to the Fick principle¹ by determining the arteriovenous difference of para-aminohippurate concentration in the peripheral arterial and the renal

TABLE I. RENAL FUNCTION STUDIES BEFORE AND AFTER BACITRACIN THERAPY—ACUTE EXPERIMENTS

NO OF PATIENT	SEX	AGE (YR)	PERIOD OF OBSERVATION	GLOMERULAR FILTRATION RATE (CC PER MIN)	RENAL PLASMA FLOW (CC PER MIN)	TUBULAR EXCRETION (MC PER MIN)	TUBULAR REABSORPTION (MM PER MIN)	FILTRATION FRACTION (1FF PER CENT)
1	M	40	Before bacitracin	133	4	-	0.185	17
			First half hour	134	816	-	0.183	16.4
			Second half hour	133	337	-	0.179	14.8
2	M	41	Before bacitracin	1.0	36	-	0.099	21.4
			First half hour	136	703	-	0.101	19.3
			Second half hour	124	600	-	0.098	20
3	M	50	Before bacitracin	1.9	80	-	0.104	22.2
			First half hour	136	386	-	0.139	26.6
			Second half hour	116	333	-	0.100	23.5
4	F	—	Before bacitracin	1.9	-	84.5	0.160	-
			First half hour	158	-	83.8	0.166	-
			Second half hour	150	-	78.4	0.157	-
5	F	3	Before bacitracin	1.3	-	80	0.091	-
			First half hour	1	-	71.5	0.090	-
			Second half hour	134	-	69.0	0.105	-

Each value
given per 1000 cc. of
2000 units of bacitracin
1000 units of bacitracin
All values have been made
between 8 a.m. and 10 a.m.

THE NEPHROTOXICITY OF BACITRACIN* IN MAN

A. J. MICHEL, M.D., H. A. ZINTEL, M.D., R. A. MA, I. S. RAVEN, M.D.,
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*(From the Harris Department of Surgical Research, Schools of Medicine
University of Pennsylvania)*

THE nephrotoxicity of parenterally administered bacitracin in animals has been well established.¹⁻³ The degree of nephrotoxicity of systemically administered bacitracin in man, however, has not been definitely confirmed. Scudt Caret and Antopol² concluded that bacitracin produced serious renal damage in mice but that it was considerably less nephrotoxic in monkeys. In monkeys necrotic renal tubule cells were found in two of the five animals studied. In 103 patients who had received bacitracin systemically for the treatment of surgical infections the evidences of nephrotoxicity were not conclusive.⁴ Phenolsulfonphthalein excretion tests, determinations of urea nitrogen or nonprotein nitrogen concentration in the blood and frequent urinalyses in a number of these patients did not demonstrate definite impairment of renal function.⁴⁻⁵ Renal damage was suspected, however, because of the frequent occurrence of albuminuria, the less frequent appearance of cellular elements and casts in the urine and the occasional development of oliguria or anuria. It was not possible to state categorically whether the oliguria or the anuria observed was the result of bacitracin therapy, the infectious process or whether they were the sequelae of anesthesia and operation.

It was thought advisable to determine the functional capacity of the kidney before and after parenteral bacitracin therapy in patients who did not have infections. Glomerular filtration rate, maximal tubular reabsorption of phosphate, maximal tubular excretion of para-aminohippurate and renal plasma flow were determined before and after systemic bacitracin therapy in ten volunteer, convalescent surgical patients with no signs or symptoms of infection or renal disease and no prior evidence of functional renal impairment.

PROCEDURE

Sodium thiosulfate was used to measure the glomerular filtration rate. Maximal tubular reabsorption of phosphate was determined after doubling the initial blood phosphate concentration.⁶ Maximal tubular excretion and effective renal plasma flow were determined, the former at high and the latter at low blood para-aminohippurate concentrations.⁷ All blood samples for these determinations were taken from an indwelling arterial needle. Unaltered changes in blood concentrations were prevented by a constant intravenous infusion of the agents used.

Percent of
mg

York

In the five patients of the acute experimental group glomerular filtration rate and maximal tubular reabsorption of phosphate were measured for three consecutive ten minute periods before bacitracin was administered. Then 2,000 units of bacitracin were administered intravenously in one to two minutes followed by the administration of 260 units of bacitracin per minute for approximately one hour. During the latter period the same renal function studies were repeated for six consecutive ten minute periods. As effective renal plasma flow and maximal excretion of para aminohippurate cannot be measured simultaneously the former renal function was determined in Patients 1, 2 and 3 and the latter in Patients 4 and 5.

In the "chronic" experiments all of the renal functions described were determined in each of the six patients before and after the intramuscular administration of bacitracin. Patients 1, 2, 3, 4 and 5 received 49,000 to 50,000 units of bacitracin every six hours for four to thirteen days. Patient 6 received three doses of 50,000 units of bacitracin intramuscularly for two consecutive days, none for the next six days, and then four injections of 50,000 units each in the twenty four hours preceding the final renal function tests. In two patients, 1 and 3, the studies were repeated two and four weeks respectively after the administration of bacitracin had been discontinued. After bacitracin therapy in Patient 5 the total renal plasma flow was also measured according to the Fick principle¹⁰ by determining the arteriovenous difference of para aminohippurate concentration in the peripheral arterial and the renal

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NO OF PATIENT	SEX	AGE (YR.)	PERIOD OF OBSERVATION	GLOMERULAR FILTRATION RATE (ml/min)	RENAL PLASMA FLOW (ml/min)	TUBULAR EXCRETION (%)	TUBULAR REABSORPTION (%)	FILTRATION FRACTION (%)
1	M	40	Before bacitracin First half hour Second half hour					
2	M	41	Before bacitracin First half hour Second half hour	120 136 144	562 703 600	— — —	0.039 0.101 0.085	21.4 19.3 20.7
3	M	50	Before bacitracin First half hour Second half hour	149 136 146	580 584 535	— — —	0.104 0.133 0.100	22.2 26.6 23.5
4	F	27	Before bacitracin First half hour Second half hour	154 178 150	— — —	84.5 83.8 78.4	0.160 0.166 0.157	— — —
5	F	31	Before bacitracin First half hour Second half hour	143 144 134	— — —	80.7 71.5 69.0	0.091 0.090 0.105	— — —

Filtration rate on period after 200 units of bacitracin.

All values have been made between 94 and 99.

THE NEPHROTOXICITY OF BACITRACIN* IN MAN

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PROCEDURE

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In the five patients of the acute experimental group glomerular filtration rate and maximal tubular reabsorption of phosphate were measured for three consecutive ten minute periods before bacitracin was administered. Then 2 000 units of bacitracin were administered intravenously in one to two minutes followed by the administration of 360 units of bacitracin per minute for approximately one hour. During the latter period the same renal function studies were repeated for six consecutive ten minute periods. As effective renal plasma flow and maximal excretion of para aminohippurate cannot be measured simultaneously the former renal function was determined in Patients 1, 2 and 3 and the latter in Patients 4 and 5.

In the 'chronic' experiments all of the renal functions described were determined in each of the six patients before and after the intramuscular administration of bacitracin. Patients 1, 2, 3, 4 and 5 received 49 000 to 50 000 units of bacitracin every six hours for four to thirteen days. Patient 6 received three doses of 50 000 units of bacitracin intramuscularly for two consecutive days none for the next six days and then four injections of 50 000 units each in the twenty four hours preceding the final renal function tests. In two patients 1 and 3, the studies were repeated two and four weeks respectively after the administration of bacitracin had been discontinued. After bacitracin therapy in Patient 5 the total renal plasma flow was also measured according to the Fick principle¹⁰ by determining the arteriovenous difference of para aminohippurate concentration in the peripheral arterial and the renal

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NO OF PATIENT	SEX	AGE (YR)	PERIOD OF OBSERVATION	GLOMERULAR FILTRATION RATE (CC PER MIN)	RENAL PLASMA FLOW (CC PER MIN)	TUBULAR EXCRETION (MG PER MIN)	TUBULAR REABSORPTION (MG PER MIN)	FILTRATION FRACTION (PER CENT)
1	M	40	Before bacitracin	133	174	---	0.185	17.2
			First half hour	134	216	---	0.183	16.4
			Second half hour	133	237	---	0.179	14.8
2	M	41	Before bacitracin	120	62	---	0.099	21.4
			First half hour	136	703	---	0.101	19.3
			Second half hour	124	600	---	0.098	10.7
3	M	40	Before bacitracin	119	180	---	0.104	22.2
			First half hour	126	186	---	0.119	26.6
			Second half hour	126	230	---	0.100	13.5
4	F	22	Before bacitracin	129	---	84.7	0.160	---
			First half hour	128	---	93.8	0.166	---
			Second half hour	120	---	78.4	0.157	---
5	F	33	Before bacitracin	123	---	80.7	0.091	---
			First half hour	122	---	71.3	0.090	---
			Second half hour	134	---	61.0	0.102	---

F values recorded are the average of three consecutive ten minute blood flow and filtration periods. After determination of renal plasma flow.

venous blood Two different lots of commercially prepared bacitracin were administered to these patients The lots are identified as lots A and B

RESULTS

Acute Experiments—The results of the determinations in the acute experiments are shown in Table I The values before the administration of bacitracin are the average values of three determinations and likewise the values for the first half hour and the second half hour periods are average values of three determinations done during these periods No statistically significant changes were observed in the renal functions studied in the acute experiments since a significant change would be a change greater than the allowed experimental error of plus or minus 10 per cent However, the

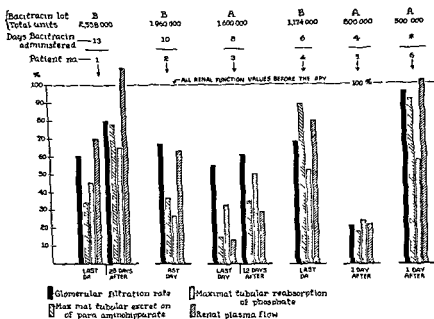


Fig 1—Graphic representation of per cent of the various kidney functions remaining after bacitracin therapy as compared to kidney functions before bacitracin therapy in the chronic experiments

Patient 6 did not receive bacitracin continuously. He received 1,000,000 units of bacitracin daily for two consecutive days, none for the next six days, and then 200,000 units in the twenty-four hours preceding the renal function studies shown here

progressively diminishing values for maximal tubular excretion of para amino hippurate in Patients 4 and 5 (the only patients in whom this study was done in the acute experiments) are suggestive of early tubular damage The increases in the filtration fractions from 17.2 to 24.8 per cent and 22.2 and 26.6 per cent respectively in Patients 1 and 3 are probably evidences of a slight adrenergic effect and do not represent a diminished ability to secrete para aminobipparate at the blood concentration employed

Chronic Experiments—A moderate to very severe reduction in all of the renal functions studied was observed in all but one of the six patients who had received bacitracin from four to thirteen days The average values of the

renal functions in the "chronic" experiments are shown in Table II. Each recorded value represents the average of three consecutive observations. Fig. 1 shows the changes in renal function graphically with the values before bacitracin administration equated to 100 per cent. In the five patients who received the bacitracin without interruption the decrease in glomerular filtration rate varied from 32 to 79 per cent below the values obtained before bacitracin. Effective renal plasma flow was decreased 20 to 87 per cent, maximum tubular excretion of para aminohippurate 11 to 85 per cent and maximal tubular reabsorption of phosphate 48 to 73 per cent. In Patient 5 the effective renal plasma flow was decreased 71 per cent below the value observed before the administration of bacitracin. However assuming the total renal plasma flow in the patient to be normally 4 per cent greater¹¹ than the effective renal plasma flow, then the total renal plasma flow after bacitracin was reduced only 50.5 per cent.

DISCUSSION

The maximal secretory or reabsorptive capacity of the renal tubule is an inherent property of the tubular cell and under standard conditions is relatively constant.² The decreases in the maximal tubular excretion of para aminohippurate and of the maximum tubular reabsorption of phosphate represent absolute decreases in renal function. Previous work has demonstrated that as tubular efficiency is impaired the glomerular filtration rate and renal plasma flow also decrease.^{1, 12}

In the acute experiments the gradual decline of values obtained for maximal tubular excretion of para aminohippurate in Patients 4 and 5 suggests beginning tubular damage. The variations of maximal tubular reabsorption of phosphate, however, are not uniform throughout the acute experiments. The data suggest that the renal enzyme engaged in the transport of phosphate across the tubular cell is more resistant to the effects of bacitracin than the enzyme involved in the secretion of para aminohippurate. The early minimal evidences of change in maximal tubular excretion are in accord with the clinical observations since casts and albumin usually do not appear in the urine before the second or third day of parenteral bacitracin therapy.⁴

It has been previously reported that thiosulfate inhibits the antibiotic action of bacitracin.⁴ Since bacitracin and sodium thiosulfate were introduced intravenously in the same solution in the acute experiments, it became necessary to determine whether 0.3 mg. per cubic centimeter of sodium thiosulfate would inhibit the activity of 1.2 units per cubic centimeters of bacitracin in the same solution over a period of one hour at room temperature. An aqueous solution containing these concentrations of bacitracin and sodium thiosulfate was allowed to stand at room temperature. At one, two, four and eight hour intervals the antibacterial activity of this solution was determined by the plate cup method using a standard strain of *Micrococcus flavus*. The results are compared in Table III with those obtained with an aqueous solution of 1.2 units of bacitracin per cubic centimeter and with an aqueous solution containing 0.3 mg. per cent sodium thiosulfate. The antibacterial action of

the bacitracin solution and the antibacterial action of the solution of bacitracin and sodium thiosulfate combined were essentially equal. The sodium thiosulfate solution alone had one half the antibacterial activity of the bacitracin solution as measured directly on the culture media.

TABLE III. ZONES OF INHIBITION OF BACTERIAL GROWTH BY BACITRACIN AND SODIUM THIOSULFATE AVERAGES OF TRIPPLICATE DETERMINATIONS

TIME AT ROOM TEMPERATURE (HR.)	1:1 PER C C OF BACITRACIN ALONE (MM.)	0.5 MG. PER C C OF SODIUM THIOSULFATE ALONE (MM.)	BACITRACIN AND SODIUM THIOSULFATE MIXTURE (MM.)
1	19.0	10.5	18.5
2	18.3	10.5	18.0
4	17.3	11.5	16.8
8	17.0	1.0	14.5

From the data obtained it is not possible to state whether any of the bacitracin was actually inhibited. However the data do indicate that only a small fraction of the bacitracin could have been inhibited in the solution administered.

The reduction in effective renal plasma flow in the chronic experiments in Table II and Fig. 1 probably does not indicate similar decrements in total renal plasma flow. In Patient 5 the renal extraction ratio as measured by differences in concentration of para-aminohippuric acid in arterial blood and renal vein blood (by direct catheterization) indicates that only 45.6 per cent of the para-aminohippuric acid was removed in one renal circulation instead of the expected 92 to 96 per cent.¹¹ Thus the total renal plasma flow is probably 50 to 60 per cent greater than the effective renal plasma flow after bacitracin. Conversely the decrement in total renal plasma flow is approximately one-half that in the effective renal plasma flow.

In the chronic experiments the increased volume of glomerular filtrate in relation to tubular function which was consistently observed in the 'chronic' experiments indicates that bacitracin predominately affects the tubular epithelium. The data from Patient 6 who received bacitracin for two days, none for the next six days, and then again received bacitracin the day before the renal function tests were repeated are rather interesting. It would appear that his kidneys had recovered from the effects of the two days of bacitracin administration and that the marked diminution of tubular excretion of para-aminohippurate was the result of the bacitracin he received in the twenty-four hours immediately preceding the final renal function tests. The data of Patients 1 and 5 probably indicate that relatively few glomeruli continue to function when their tubules become inactive. In Cases 5 the difference between the total renal plasma flow and the effective renal plasma flow represents the volume of plasma perfusing damaged inert renal tissue.

CONCLUSIONS

1. The administration of 23,600 units of commercial bacitracin intravenously over a period of roughly one hour caused no statistically significant

cant changes in glomerular filtration rate maximal tubular excretion of para aminohippurate, or maximal tubular reabsorption of phosphate of renal plasma flow. However, there was a gradual decrease in the average values for maximal tubular excretion of para aminohippurate which were suggestive of early tubular damage.

2 The commercial bacitracin used in five "chronic" experiments in a dosage of 49 000 to 50 000 units intramuscularly every six hours for four to thirteen days produced moderate to very severe renal damage. The one patient of the "chronic" experimental group who received bacitracin for two days, none for six days and then again received bacitracin for one day before the renal function tests were repeated showed marked impairment in tubular excretion of para aminohippurate but no significant diminution in the remaining renal functions.

3 Two of the five patients of the chronic experimental group showed evidences of considerable recovery of the renal functions studied twelve days and twenty-eight days after bacitracin was discontinued.

4 The data indicate that bacitracin predominantly affects the tubular epithelium.

REFERENCE.

- 1 Seudt J V and Antopol W. Some Pharmacological Characteristics of Bacitracin. *Annals of the New York Academy of Sciences* 46: 1017-1027 (1945).
- 2 Seudt J V and Antopol W. The Effect of Bacitracin on the Excretion of Iodine-131 in the Urine of Normal Man. *Annals of the New York Academy of Sciences* 46: 1028-1037 (1945).
- 3 Seudt J V and Antopol W. The Effect of Bacitracin on the Excretion of Iodine-131 in the Urine of Normal Man. *Annals of the New York Academy of Sciences* 46: 1038-1047 (1945).
- 4 Seudt J V and Antopol W. The Effect of Bacitracin on the Excretion of Iodine-131 in the Urine of Normal Man. *Annals of the New York Academy of Sciences* 46: 1048-1057 (1945).
- 5 Seudt J V and Antopol W. The Effect of Bacitracin on the Excretion of Iodine-131 in the Urine of Normal Man. *Annals of the New York Academy of Sciences* 46: 1058-1067 (1945).
- 6 Seudt J V and Antopol W. The Effect of Bacitracin on the Excretion of Iodine-131 in the Urine of Normal Man. *Annals of the New York Academy of Sciences* 46: 1068-1077 (1945).
- 7 Seudt J V and Antopol W. The Effect of Bacitracin on the Excretion of Iodine-131 in the Urine of Normal Man. *Annals of the New York Academy of Sciences* 46: 1078-1087 (1945).
- 8 Seudt J V and Antopol W. The Effect of Bacitracin on the Excretion of Iodine-131 in the Urine of Normal Man. *Annals of the New York Academy of Sciences* 46: 1088-1097 (1945).
- 9 Seudt J V and Antopol W. The Effect of Bacitracin on the Excretion of Iodine-131 in the Urine of Normal Man. *Annals of the New York Academy of Sciences* 46: 1098-1107 (1945).
- 10 Seudt J V and Antopol W. The Effect of Bacitracin on the Excretion of Iodine-131 in the Urine of Normal Man. *Annals of the New York Academy of Sciences* 46: 1108-1117 (1945).
- 11 Seudt J V and Antopol W. The Effect of Bacitracin on the Excretion of Iodine-131 in the Urine of Normal Man. *Annals of the New York Academy of Sciences* 46: 1118-1127 (1945).
- 12 Seudt J V and Antopol W. The Effect of Bacitracin on the Excretion of Iodine-131 in the Urine of Normal Man. *Annals of the New York Academy of Sciences* 46: 1128-1137 (1945).
- 13 Seudt J V and Antopol W. The Effect of Bacitracin on the Excretion of Iodine-131 in the Urine of Normal Man. *Annals of the New York Academy of Sciences* 46: 1138-1147 (1945).
- 14 Seudt J V and Antopol W. The Effect of Bacitracin on the Excretion of Iodine-131 in the Urine of Normal Man. *Annals of the New York Academy of Sciences* 46: 1148-1157 (1945).
- 15 Seudt J V and Antopol W. The Effect of Bacitracin on the Excretion of Iodine-131 in the Urine of Normal Man. *Annals of the New York Academy of Sciences* 46: 1158-1167 (1945).

LOCAL REACTION TO OXIDIZED CELLULOSE AND GELATIN HEMOSTATIC AGENTS IN EXPERIMENTAL CONTAMINATED RENAL WOUNDS

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EXPERIENCE with patients in whom abscesses formed in renal wounds after the use of Oxycel* for bolsters and for hemostasis led us to doubt the reports of the benign nature of this foreign substance. Then MacDonald and Matthews in 1947 published their study of absorbable hemostatics in experimental nephrotomy incisions with the conclusion that these substances were easily and rapidly absorbed. We felt, however, that their conclusions were not applicable to clinical urology because such incisions are seldom made in uninfected kidneys but are usually made for stone obstruction or focal infection. We, therefore, began a series of experiments to compare the healing of contaminated renal wounds which were packed with absorbable hemostatic with similar wounds not packed.

MATERIALS AND METHODS

Young rabbits were chosen because of their known resistance to adventitiously introduced infection and because of their availability. After preoperative administration of atropine anesthesia was obtained with drop ether. The lumbar approach to the kidneys was used (Fig 1 a) and the right side was closed before the left incision was made. The right kidney was lifted into the wound the edges of which were protected by gauze packs. A long coronal nephrotomy incision was made from pole to pole extending approximately half way to the pelvis; the calyx was not purposely entered. Brisk bleeding was invariably encountered. A piece of Gelfoam† 3 by 2 by 15 cm. or folded Oxycel of the same general dimensions was inserted into the wound and two mattress sutures of 0000 chromic catgut swedged on cutting edge needles were placed in the capsule such that hemostasis was effected (Fig 1 b). Using a blunted 22 gauge needle 0.1 cc. of dilute autogenous fecal suspension was injected beneath the pack. The flank wound was closed with continuous cotton sutures. A similar procedure was done on the left side except that hemostasis was secured by the two mattress sutures without packing; an equal amount of fecal suspension was injected. The animals were then killed by decapitation at selected intervals (from three days to three weeks), and autopsy was performed after preparing the abdomen as for the original operation. Through separate incisions each kidney and an adjacent portion of the body musculature was removed with sterile technique. Section (Fig 1, c) was made in each kidney at right angles to the nephrotomy incision so that smears, cultures and photographs could be

nade before the specimen was fixed in 10 per cent formalin. Serial hand sections were then cut and the most altered portions sent for imbedding, sectioning and staining with hematoxylin and eosin.

RESULTS

Thirty nine rabbits were operated upon (Table I). Of these 2 died spontaneously and when discovered were too autolysed for study. Of the remaining 37, 23 had a gross abscess in the right (treated) nephrotomy incision and no abscess on the left. Seven had abscesses on the right and in addition had a healing infarcted area on the left which lacked acute inflammatory response. Four had abscesses on the left which were smaller than those on the pael side and 2 had larger ones on the left. In one animal (twenty-one days) neither side contained an abscess.

The first and largest group consisting of 23 animals was Group A (Table I) in which the abscess developed only on the right. The photograph (Fig 2) shows a typical result (Rabbit 15 Gelform prel killed at fourteen days) a

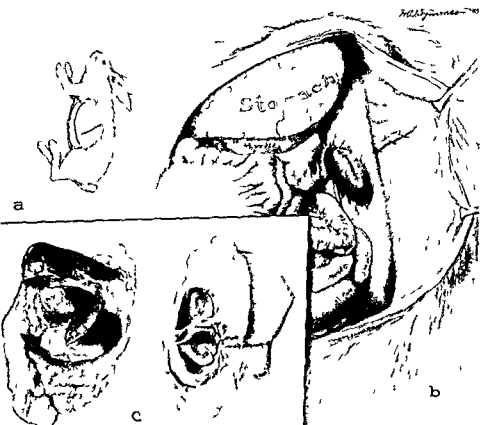


Fig 1—*a* Operative incision (oblique) and autopsy incision (curved). *b* Unpacked (left) kidney in situ. *c* Right and left kidneys opened up, showing abscess on right scar of incision on left. (Rabbit 4 Gelform prel killed at fourteen days)

large abscess filled with creamy pus in the right kidney (a) and a thin white line marking the line of the incision on the left (a'). Cultures showed non hemolytic *Staphylococcus albus* bilaterally. As seen on the low power (b) and high power (c) photomicrographs the right kidney is involved in an acute inflammatory process with abscess formation. Five zones are distinguished: compressed renal tissue, dilated tubular area, fibrous barrier, pus, and involved tinfoilm—in that order from outside in. On the left (b, c) on the contrary, there is a thin line of repair tissue without inflammation. A similar result (Fig. 3) was found in Rabbit 3, killed at fourteen days. In 21 other cases similar changes were found.

TABLE I. RELATION OF INCIDENCE OF ABSCESS TO PRESENCE OF HEMOSTATIC AGENT

GROUP DESCRIPTION	SITE OF ABSCESS		TOTAL ANIMALS	PERCENTAGE IN GROUPS
	RIGHT (PACKED) KIDNEY	LEFT (UNPACKED) KIDNEY		
A. Right abscess Left negative	23	0	23	100
B. Right abscess Left infarcted area	-	0 (infarction in)	-	-
C. Bilateral abscess	1	6	7	100

A second group (Group B Table I) is made up of those animals with a well developed abscess on the right and with a zone of infarction about the line of incision on the left. Rabbit 33 (Oxcel pack killed at fourteen days) is characteristic. The photograph (Fig. 4) shows the large pus filled abscess and hematoma on the right (a) and the smaller pale infarcted area on the left (a'). Microscopic sections show the great polymorphonuclear cell reaction about the right abscess (b and c) and the almost complete absence of acute inflammatory reaction in the infarcted area on the left (b and c). The detail of this intense polymorphonuclear cell response on the right is seen in d while faded autolysed cells without inflammatory reaction are found in d. Essentially this same picture was seen in the remaining 6 cases of this group and was doubtless due to severance of the blood supply by the incision.

One other group must be mentioned (Group C Table I). In 4 cases acute inflammatory reaction with abscess formation took place on both sides and in 2 cases it was more severe on the left than on the right. The interpretation is that in overwhelming doses of organisms was administered followed by infarction or hematoma formation.

There was little to differentiate the effects of tinfoilm and Oxcel nor did breakdown into duration before autopsy show significant differences (Table II). The rather high percentage of positive cultures on the untreated side (Table III) indicates that in many unpacked incisions tissue infection was present but since it was being handled by the local defense mechanisms without hindrance by foreign material accumulation of bacteria and pus did not occur. Analysis of infecting organisms gave no indication that any particular bacterium increases the likelihood of abscess formation about the pack (Table IV). Mixed infections occurred in 22 kidneys.

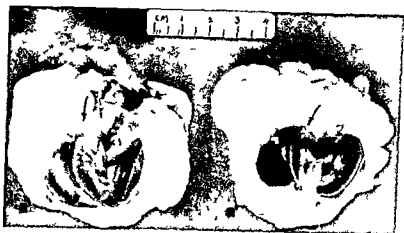


Fig 2—*a* Pig kidney with abscess. *b* Cross section of right incision with abscess ($\times 5$). *b* Cross section of left incision ($\times 5$). *c* Detail of *b* showing interstices of Gelfoam filled with pus ($\times 30$). *d* Detail of *b* showing healing scar ($\times 45$). (Rabbit 15 Gelfoam pack killed after fourteen days.)

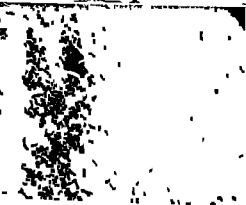


Fig 3—*a* Right kidney with abscess *a* left kidney with healing incision similar to
Fig 2 *b* and *b* ($\times 5$) cross sections of wound *c* and *c* ($\times 4$) *d* tail of *a* and *b* (I abbt
3 Gelfoam pack killed at fourteen days.)

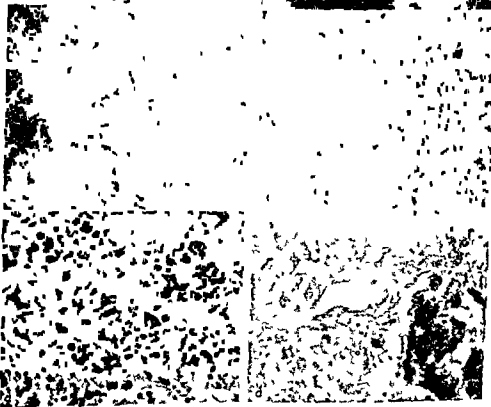


FIG. 4.—(Fol. 1 and 2 of 100)

TABLE II INCIDENCE OF ABSCESS IN RELATION TO TYPE OF HEMOSTATIC AGENT AND TO DURATION OF INFECTION

DAYS	ABSCESS ON PACKED SIDE ONLY		BILATERAL ABSCESSES	
	GELFOAM	OXYCEL	GELFOAM	OXYCEL
to 5	-	1	-	-
7	-	3	-	-
14	8	7	-	4
21	3	-	-	-
Total cases	11	11	-	4

TABLE III INCIDENCE OF POSITIVE CULTURES IN RIGHT (PACKED) AND LEFT (UNPACKED) KIDNEYS

	RIGHT	LEFT
Growth	84% (31 cases)	51% (22 cases)
No growth	16% (6 cases)	41% (15 cases)

TABLE IV INFECTING ORGANISMS BY GROUP

Organism	GROUP				C	
	A		B		(CASES)	
	1	2	1	2	1	2
Alpha Streptococcus	-	4	1	0	1	1
Diphtheroid	-	1	1	2	0	0
Beta Streptococcus	2	-	1	0	-	0
Staphylococcus aureus	-	0	0	0	1	0
Gamma Streptococcus	-	0	1	1	0	0
Proteus vulgaris	-	0	1	0	0	0
Pseudomonas aeruginosa	0	1	0	0	0	0
Hemolytic Staphylococcus albus	0	1	0	0	0	0
Anaerobic Streptococcus	1	0	0	0	0	0
Anaerobic Streptococcus	0	1	0	0	0	0

DISCUSSION

Statistically significant conclusions are reached which confirm good surgical teaching, that any foreign body, however nonreactive and absorbible is detrimental to wound healing especially in the presence of infection. Although Jenkins and co-workers had warned that bulky gelatin sponges may become rapidly liquefied and offer a culture medium which may influence the development of infection and others (Uhlen and co-workers, Goldstein and Hollander and Merrieks) felt that large amounts should be avoided most workers found no contraindication to the use of these substances in contaminated wounds. The strongest warning came recently when Lufmann and Method demonstrated experimentally the adverse effect of absorbible hemostatic agents in bowel anastomosis. The present study confirms the opinions of those who would limit the use of these substances in the presence of infection.

SUMMARY

To test the reactivity of absorbible hemostatic agents in contaminated wounds 39 rabbits were subjected to extensive bilateral nephrotomy incisions.

Fig. 4—*a* Right kidney with abscess, *b* left kidney with abscess, *c* and *d* cross sections of wound (X) *e* and *f* detail of abscess reaction *a* and *b* (X10) *c* and *d* cellular detail of *a* and *b* (X400) showing leucocyte polymorphonuclear cell reaction on the right and vague autolyzed tubular cell on the left, without inflammatory reaction (Rabbit 33 Oxyvel pack, killed at fourteen days).

contaminated with a suspension of autogenous feces. The right incision in each animal was closed over an Oxycel or Gelform pack, the left was merely closed.

Abscesses were almost constantly found in the right (packed) kidney (in 36 of 37 animals), and infrequently found on the left (unpacked) side (6 of 37 animals). Two rabbits were discarded because of post mortem autolysis and one showed bilateral healing.

The interpretation is made that these agents should be used sparingly in clinical nephrotomy incisions and at other sites in urologic surgery since such wounds are commonly contaminated by infected urine.

REFERENCES

Goldstein, A. E., and Hollander, A.: Experiences With Oxycel Gauze in Genito-urinary Surgery J Urol 59: 195-201, 1948

" " Kidney Wounds J Urol 57: 80-81, 1947

Merrick*, J. W. in Urologist's Correspondence Club Letter May 1, 1948

Uihlein, A., Claggett, O. T. and Osterberg, A. E. Use of Oxidized Cellulose for Hemostasis in Surgical Procedures Proc Staff Meet Mayo Clin 20: 29-32, 1945

SPONTANEOUS EXTERNAL BILIARY FISTULAS

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A SPONTANEOUS external biliary fistula was observed recently which opened through the abdominal wall in the midline above the umbilicus. Because of the rarity of this type of fistula it is reported with a brief review of the literature.

CASE REPORT

History.—A 61-year-old obese white woman, aged 72 years, was admitted to the University of Kansas Medical Center, Nov. 4, 1947, complaining of an opening in the abdominal wall which had been present one and one-half years. The patient first noticed a painless, soft, round swelling in the midline approximately two inches above the umbilicus. This swelling gradually increased in size, became more superficial, and after three months ruptured to the outside spontaneously, discharging a yellowish pus which was nonirritating and essentially odorless. The quantity of drainage was rather copious at first but it soon decreased, persisting as only a slight constant ooze.

Physical Examination.—There was an opening in the midline of the abdomen 3 to 4 mm. in diameter located 5 cm. above the umbilicus. From the opening which had the appearance of a sinus, small quantities of yellow, purulent material could be expressed. A small paraumbilical hernia was present. This hernia was easily reducible. The blood pressure was 110 systolic and 80 diastolic. The remainder of the physical examination was within normal limits for a woman of 72 years of age. A scout film of the abdomen revealed an irregular area of increased density measuring 3 by 4 cm. which was constant in size, shape, and position with that of a calcified gall bladder. X-ray studies showed a normal gastrointestinal tract. Lipiodol injection of the sinus tract permitted a more complete visualization of the calcified structure in the upper right quadrant. The lipiodol passed into the intestine (Fig. 1). It was the roentgenologist's opinion that the dye entered the duodenum. A diagnosis of biliary fistula was made.

Operative Note.—A right transrectus incision was made near the midline above the level of the umbilicus. The gall bladder was partially calcified and filled with stones. Extending from the fundus of the gall bladder there was a fistulous tract which passed through the fat of the falciform ligament to and through the abdominal wall in the midline. The common duct and the common hepatic duct were stretched and anastomosed to form an inverted Y (Fig. 2). There was an anomalous right hepatic artery which lay near the cystic duct. The gall bladder was removed and the paraumbilical hernia was repaired through the abdominal incision.

The pathologist's report was acute and chronic fibrous cholecystitis and pericholecystitis with calcification, cholelithiasis, and chronic periportal hepatitis.

Thilesius in 1670¹ is generally credited with reporting the first case of biliary fistula due to perforation of gallstones through the abdominal wall. In 1890 Courvoisier² published a collection of 499 cases of perforation of the gall bladder, 109 of which were listed as spontaneous fistulas through the abdominal wall. Naunyn³ recorded 184 cases in 1896 and in 1897 Bonnet⁴ collected 122 cases. Since the reviews of Naunyn and Bonnet indicated that some of the diagnoses were founded upon clinical impressions and not proved by operation or autopsy, we have accepted Courvoisier's summary as probably most accurate and have added case reports from 1890 to June 1948 (Tables I and II).

contaminated with a suspension of autogenous feces. The right incision in each animal was closed over an Oxyeel or Gelfoam pack, the left was merely closed.

Abscesses were almost constantly found in the right (packed) kidney (in 36 of 37 animals), and infrequently found on the left (unpacked) side (6 of 37 animals). Two rabbits were discarded because of post mortem autolysis and one showed bilateral healing.

The interpretation is made that these agents should be used sparingly in clinical nephrotomy incisions and at other sites in urologic surgery since such wounds are commonly contaminated by infected urine.

REFERENCES

- Goldstein, A. E., and Hollander, A.: Experiences With Oxyeel Gauze in Genito-urinary
Surgery, J. Urol. 59: 600, 1948.

subsequent perforation and fistula formation was much higher. This at present seems the best explanation of the greater number of cases collected in earlier years.

TABLE I. LOCATIONS OF PERFORATIONS

COURVOISIER			CASES SINCE 1890	
In r Hypochondrium	40	80	Rt upper quad	11
Am Pand der r Rippenbogen	38			
In r Mesogastrium	17	27	It lower quad	4
In r Regio ilica	10		Epigastrium	0
In Epigastrium	6	6		
In der Nähe des Nabels	26	39	Umbilicus and region of umbilicus	1
Im Nabel	12			
Unter dem Nabel	11	11	Below umbilicus	4
In linker Leiste	1	1	Left flank	2
Multiple	1	1	Multiple	1
			It flank	1
			It thigh	2
169				37

Spontaneous external biliary fistula as a complication of cholecystitis is chiefly a disease of women of the older age group in the fifth to seventh decades. This predilection for women is unquestionably a reflection of the higher incidence of cholecystitis in women as compared with men.

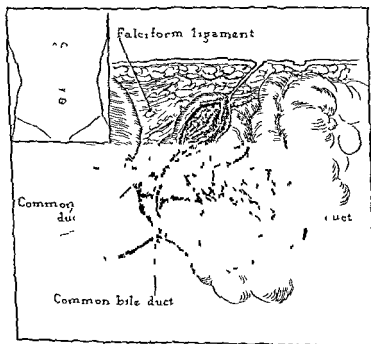


Fig. — Sketch showing gall bladder, bile duct, and sinus tract to abdominal wall. Location of fistulous opening is shown in inset.

The fistulous site, usually single, is found most frequently in the right upper quadrant of the abdominal wall. In certain cases the fistula has been directed by the falciform ligament to the region of the umbilicus in the midline. Other more distant points of fistulous openings in the abdominal wall

Spontaneous biliary fistula usually arises as a result of gallstones and suppurative cholecystitis. Inflammatory adhesions form between the gall bladder fundus and the abdominal parietes. A perforation at the point of contact discharges pus within the substance of the abdominal wall, forming an abscess. At length the abscess burrows through the skin establishing communication between the fundus and the exterior. Long fistulous tracts may develop within the abdomen and eventually perforate through the skin. These

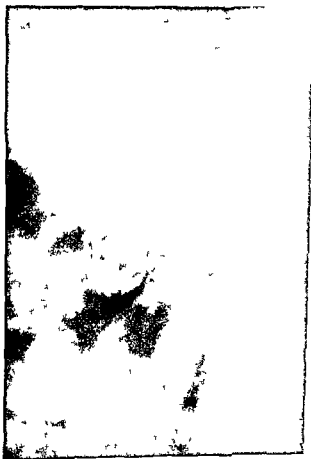


Fig 1—Radiograph showing tube in a sinus tract with contrast medium in gall bladder, common bile duct and duodenum

fistulas usually arise from the fundus of the gall bladder rather than from one of the ducts. It is not uncommon to find that the perforation in the gall bladder wall has become sealed after expulsion of pus and stones through the abdominal wall and a sinus tract persists.

From a review of the literature it becomes apparent that prior to the

In those instances where lipiodol injection of the fistulous tract was attempted, a partial visualization of the biliary ducts and first portion of the duodenum was obtained. This procedure is recommended as a reliable pre operative diagnostic aid, but its efficacy is obviously dependent upon the patency of the cystic duct.

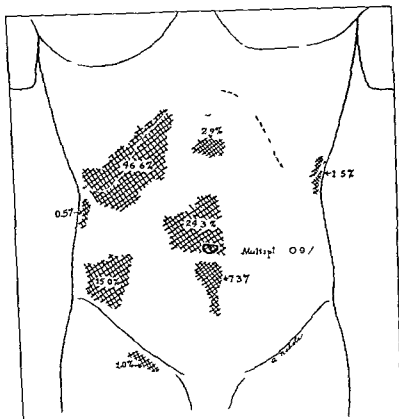


Fig 3 -Sketch showing location of 106 external biliary fistulas in percentages of total number

After expulsion of calculi or their extraction by suitable operative procedures many fistulas have healed spontaneously. The present day treatment, that of cholecystectomy with excision of the tract in its entirety is the therapy of choice.

SUMMARY

A case of spontaneous perforation of the gall bladder through the mid line of the abdominal wall is reported. A total of 205 cases of external biliary fistula have been found in the literature. 36 of which have been recorded since 1890.

Spontaneous external biliary fistulas are rare. It is probable that such fistulas were more common before cholecystostomy and cholecystectomy became the accepted treatment of gall bladder disease.

Early literature on abdominal biliary fistulas is somewhat confusing because of inaccuracies of diagnosis.

TABLE II LIST OF PUBLISHED CASES OF SPONTANEOUS LATERAL PERFORATION OF THE GALL BLADDER SINCE 1890

Author	Year	Age	Sex	Location	Spont. healing	Excision and drainage	Spont. healing
Colegrove ⁷	1891	83	F	Umbilicus	Yes	Yes	Spont healing
Knoop ⁸	1892	32	F	Below umbilicus	Yes	Yes	Incision and drainage with spont healing
		62	F	Above umbilicus	Yes	Yes	Incision and drainage with spont healing
Guepin ⁹	1894	76	F	Rt hypochond	Yes	No	Spont healing
Bonnet ⁴	1897	50	F	Rt subcostal	Yes	No	Spont healing
Trille ¹⁰	1899	1	F	Left flank	No	Yes	Persistent
Fabricius ¹¹	1899	60	F	Umbilicus	Yes	No	Persistent
		40	F	Rt hypochond	Yes	No	Excision and healing
Porges ¹²	1900	47	F	Rt thigh	Yes	Yes	Excision and healing
Gibbon ¹³	1901	50	F	Umbilicus	Yes	Yes	Excision and drainage with healing
Pinnatelle and Horand ¹⁴	1906	53	F	Rt iliac fossa	Yes	Yes	Persistent
Abell ¹⁵	1909	23	M	Rt thigh	Yes	No	Excision and healing
	1909	60	F	Rt. lower quad.	Yes	Yes	Incision and drainage with healing
Vignard ¹⁶	1910	65	F	Umbilicus	Yes	Yes	Spont healing
Tisserand ¹⁷	1910	37	F	Umbilicus	Yes	Yes	Cholecystectomy with excision and healing
Beje ¹⁸	1915	57	F	Rt flank	Yes	Yes	Not reported
Horhammer ²⁰	1916	38	F	Pt hypochond	Yes	Yes	Excision with healing
Dyck ²¹	1920	44	F	Near umbilicus	Yes	Yes	Excision with healing
Lammer ²²	1922	67	F	Rt hypochond	Yes	Yes	Not reported
Georg ²³	1925	56	F	Rt subcostal	Yes	Yes	Not reported
Zhvanetzky	1928	27	F	Near umbilicus	Yes	Yes	Cholecystectomy with excision and healing
Zabolotny ²⁴							
Garipey ²⁵	1929	51	F	Rt subcostal	Yes	Yes	Not reported
				2-hypochond			
Davis ²⁶	1930	60	F	Multiple (1—epigastrium)	Yes	Yes	Spont. healing
McCay ²⁷	1930	74	F	Left lumbar	Yes	Yes	Cholecystectomy with excision and healing
Sachs ²⁸	1932	64	M	Rt hypochond	Yes	Yes	Persistent
Gill ²⁹	1934	74	F	Below umbilicus	Yes	Yes	Excision and healing
Adams ³⁰	1934	55	F	Hypochond	Yes	Yes	Spont. healing
Walzel ³¹	1937	54	F	Umbilicus	Yes	Yes	Excision and healing
Beguis ³²	1938	40	F	Rt iliac fossa	Yes	Yes	Persistent
Mosch ³³	1939	75	M	Above umbilicus	Yes	No	Persistent
Michaux and Mugaburn ³⁴	1941	54	F	Umbilicus	Yes	Yes	Not reported
Rankin et al ³⁵	1942	78	M	Rt subcostal	Yes	Yes	Persistent
Prulachs and Pelazo ³⁶	1944	50	F	Below umbilicus	Yes	Yes	Excision and healing
Scarpa ³⁷	1945	53	M	Pt hypochond	Yes	Yes	Persistent
Henry and Orr	1948	72	F	Above umbilicus in midline	Yes	No	Cholecystectomy with excision and healing

have been reported for example right iliac fossa (Gibbon¹³) and right thigh (Porges,¹² Abell¹⁵) Multiple fistulas may occur (Fig 3)

The nature of the discharge from the fistulas varies. Often the cystic duct has been obliterated by a stone, and only pus or viscid mucus will be emitted. In other cases the cystic duct may be patent and bile may or may not flow from the fistulous orifice. Calculi are present in nearly all cases and a history of previous biliary colic is the rule. The passage of many small stones or a solitary large stone is not uncommon.

HORMONE PREPARATIONS IN THE TREATMENT OF TWO HUNDRED EIGHTY TWO MANN WILLIAMSON DOGS

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(From the Experimental Surgery Laboratory, Harper Hospital)

INTRODUCTION

THE relation of hormones to peptic ulcer is suggested by the following. Peptic ulcer and its complications are less common in women than in men,^{1, 2} with the onset of pregnancy, ulcer symptoms as a rule disappear^{3, 4} and active peptic ulcer is extremely rare during pregnancy.^{3, 4, 5} The sex incidence of peptic ulcer in children before puberty shows a ratio of 1:1, but as the child approaches maturity the incidence is higher in the male.⁶ Peptic ulcer, not infrequently, has its onset during the climacterium,¹ and the symptoms of peptic ulcer are aggravated during the menopause.⁴ We have found also in a study of thirty women with proved duodenal ulcer that 47 per cent showed an endocrine imbalance (exclusive of menopause).⁴ It was felt therefore, that perhaps the normal female may be protected against peptic ulcer by some inherent mechanism peculiar to her sex—that a normal reproductive cycle and the increased glandular activity during active sex life and pregnancy probably serve to prevent duodenal ulcers.⁷ This naturally suggested the possibility that protection might in some way depend on hormones. We have accordingly attempted to study this question by administering various hormone preparations to dogs with the experimentally produced Mann-Williamson ulcers.

THE MANN WILLIAMSON ULCER

The Mann-Williamson ulcer^{8, 9} is a surgically produced ulcer. The pylorus is anastomosed to the jejunum 15 to 20 cm. distal to the ligament of Treitz. The duodenum is detoured into the terminal ileum about 25 cm. proximal to the ileocecal junction. A chronic ulcer nearly always develops in the jejunum opposite the stoma. Grossly and microscopically it is analogous to the postoperative jejunal ulcer following gastroenterostomy in the human being. All of our control animals died with ulcer within 135 days of the operation with an average survival of 63 days. All the layers of the intestinal wall were involved. Of the untreated animals 75 per cent died of peritonitis following perforation of the ulcers. There was very little attempt at healing.

METHOD OF STUDY

All animals were fed a diet consisting of hospital leftover foods, principally meats, with no supplements. This diet differs from the one used by Ivy¹⁰ in that Ivy and his associates used commercial dog food plus fresh ground raw hog pancreas, fresh ground raw hog liver and whole milk. We did not use this special diet because our control animals did not receive it.

Ten different series of Mann-Williamson dogs were treated parenterally. Three additional series were treated orally. (See Chart 1.) The dosage of each preparation is noted on the chart. Treatment was begun on the third or

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The unusual findings in the case here reported were (1) calcification of the gall bladder, (2) elongation and angulation of the common hepatic and common bile ducts and (3) a tortuous fistulous tract which passed from the fundus of the gall bladder through the fat of the falciform ligament and mid line of the abdominal wall above the umbilicus

REFERENCES

- 1 Thiele H. Quoted from Hirschman 20
- 2 Courvoisier, L. Pathologie und Chirurgie der Gallenwege, Leipzig 1890, F C W Vogel
- 3 Naunyn R. A Treatise on Cholelithiasis 1890, English translation by A E Garrod
- 4 Bonn 1877
- 5 Oppel. Bauchleckensteine Verhandl. d. Berl. phys. med. Gesellsch. 1877
- 6 Tajik. Abdominal Wall Tr Path Soc 18
- 7 Colegrove I. The Passage of a Large Biliary Calculus Through an Abdominal Fistula N York M J 53 131 1911
- 8 Knoop J. Callenstein im Nabel Inaugural address 9 Marburg 1861
- 9 Queper A. Volumineux calcul biliaire expulsé spontanément par une plaie de la paroi abdominale. J 7 103 1901
al ulcuse Lyon m67
- 10 1930 10
- 21 Dias E. Cholelithiasis With Biliary Fistula Discharging at Umbilicus, Arch. Phila 4 10 1920
- 22 Jammert L. Die Perforation der Gallensteine durch die Bauchdecken, 8 8 Lpz 1900
- 23 George C. Jr. Rupture of Gall Bladder J Michigan M Soc 24 50, 1905
- 24 Zhyvanetzky /abolotny, A D. A Case of Extra Gall Bladder Fistula Olesky M J 3 608 1924
- 25 Carney L. Rupture of Gall Bladder Through Abdominal Wall J A M A 92 991 1929
- 26 Davis A. Passage of Gall stones Through the Abdominal Wall Brit M J 2 41 1930
- 27 McCay F. Gallstones Passed Through Sinus in Back Brit M J 2 147 1920
- 28 Salisachs I. Spontaneous Fistulization of Gall Bladder Into the Abdominal Wall Rev de cir Barcelona 4 100, 1924
- 29 Cull E. A Case of Spontaneous External Biliary Fistula Irish J M S 6 6 1914
- 30 Adams I. The Migration and Spontaneous Delivery of a Gall Stone Through the Abdominal Wall N York North Am J 14 1-17 1914
- 31 Walzel I. Cholelith to umbilical Fistula Wien klin Wchnsch 50 709 1923
- 32 Pagnis C. Spontaneous External Biliary Fistula Bol Soc de cir de Rio de Janeiro 5 4 1918
- 33 Moschl H. Cholecystoabdominal Wall Fistula Wien klin Wchnsch 52 6 18 1918
- 34 Michan L. and Mugaburu I. Cholecystoabdominal Fistula Bol Soc arg nt de cirujanos 2 204 1941
- 35 Rankin L. J. and Bourlan H. Spontaneous External Biliary Fistula Ann Surg 116 931 1942
- 36 Paulachs I. and Pelazo M. Spontaneous Fistulization of Gall Bladder to Hypogastric Region Rev clin e pan 12 112 1944
- 37 Scarpa A. Spontaneous Fistula Due to Calculi Arch urug de med cir y e special 1

- 6 Two series of animals were each treated parenterally either with an extract prepared from urine of normal (non pregnant) women or with an extract of urine from normal men. These two extracts were prepared by the method of Krizman and Doris¹¹ which was used in the preparation of commercial pregnancy urine extract (Ant S). The urine of both normal (nonpregnant) women and that of normal men contains varying quantities of the anterior pituitary follicle stimulating hormone, estrogens and androgens.

Investigations of hormone factors not related to the reproductive system have been limited to (1) the posterior pituitary factors (Surgical Pituitrin) and (2) enterogastrone (an extract prepared from the mucosa of the small bowel of the hog). With enterogastrone one series was treated parenterally and another orally.

The therapeutic efficacy of these hormone preparations was determined by the following four criteria:

1 Comparing the average survival time of the treated animals with that of untreated controls. The 37 untreated animals lived on the average 63 days after the Mann Williamson operation.

2 Determining the percentage of treated animals that lived longer than the maximum survival time of the untreated animals. The maximum survival time of the untreated dogs was 135 days (one animal).

3 Comparing the percentage of the animals that died without ulcer in the different series. All animals in the untreated series died with the typical jejunal ulcers.

4 Comparing the percentage of ulcers in the different groups showing microscopic evidence of epithelization. Of the 25 ulcers in the untreated series examined microscopically 2 (or 8 per cent) showed epithelization.

RESULTS

It will be noted from Chart 1 that

1 The average survival time was appreciably increased in the series of animals treated parenterally with

- (a) the urine extract prepared from normal men (259 days)
- (b) the anterior pituitary like (lutemizing) hormone prepared from human pregnancy urine—Ant S (206 days)
- (c) the urine extract prepared from normal (nonpregnant) female urine (172 days) and
- (d) the anterior pituitary follicle stimulating hormone prepared from pregnant mare's serum—Gonadogen (109 days)

2 The preparations that resulted in a high percentage of animals living longer than the maximum survival time of the control animals (longer than 135 days) are

- (a) the anterior pituitary follicle stimulating hormone from pregnant mare's serum (41 per cent)
- (b) the urine extract prepared from normal (nonpregnant) woman (36 per cent)

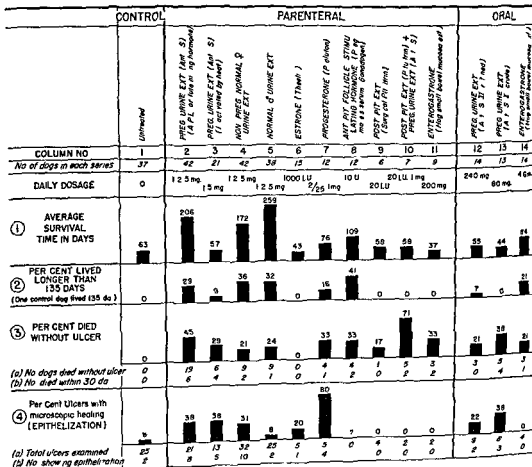


Chart 1—Hormone preparations in the treatment of Mann Williams n dogs

fourth postoperative day and was continued daily until the animal died. Death usually was due either to inanition or to peritonitis following perforation of the ulcer.

Ten of the thirteen series were treated with hormone preparations associated with the female reproductive cycle. These are:

- 1 The anterior pituitary like or luteinizing hormone prepared from human pregnancy urine—(Ant S Parke Davis & Co). One series was treated parenterally and two series were treated orally. In other series was treated parenterally with a combination of A.P.L. hormone (Ant S) and posterior pituitary extract (Surgical Pituitrin).
- 2 A heat inactivated pregnancy urine extract (Ant S heated for four hours at 90 to 95° C).
- 3 Estrone (Theelin—Parke Davis & Co).
- 4 Progesterone (Proluton—Schering Corp).
- 5 The anterior pituitary follicle stimulating hormone prepared from pregnant mare's serum (Gonadogen—Upjohn & Co).

epithelization showed evidence of healing as noted by fibroblastic proliferation and proliferation of the capillaries. These are discussed more fully elsewhere.¹

Chart I analyzes results of treatment on the basis of the four criteria just enumerated. It is evident, however, that an animal that has lived longer than 135 days might have died without an ulcer. Benefit of therapy is thus recorded in each of these two criteria. Similarly, an animal that has lived longer than 135 days might have died with an ulcer and the ulcer might have shown epithelization when it was examined microscopically. Here again the beneficial effect is recorded in each of these two criteria. If we attempt to correlate these four criteria into one (to exclude these apparent duplications) and at the same time take into consideration that death without ulcer if the animal died within 30 days is of no great significance, we note that best results were obtained in the series of animals treated with the following:

- 1 The anterior pituitary like (lutemizing) hormone of human pregnancy urine (Ant S)*
- 2 The extract prepared from urine of normal (nonpregnant) women*
- 3 The anterior pituitary follicle stimulating hormone of pregnant mare's serum (Gonadogen)
- 4 Progesterone (Proluton)
- 5 The extract from urine of normal men*

The name Anthelone (Greek *anti* against and *helkos* ulcer) was given to the anti-ulcer factor in urine which has a beneficial effect against the Mann-Williamson ulcers.¹⁵

DISCUSSION AND SUMMARY

Our studies have attempted to determine the effect on experimental Mann-Williamson ulcers of certain major hormones which are concerned in the reproductive cycle. It is well known that the hormones of the anterior pituitary activate the gonads and the gonads, in response to this stimulation, elaborate their own internal secretions. These internal secretions (that is, androgens and estrogens) are all excreted in the urine of men and women in pregnancy and in nonpregnant states though in varying degrees. The anterior pituitary principles (lutemizing and follicle stimulating) the corpus luteum hormone (progesterone) and the urine extracts from normal women and men (Anthelone) appeared to be of greatest value in the healing of the experimental Mann-Williamson ulcers. Estrogens were without benefit.

The study is admittedly not complete and the results not definitely conclusive. Our findings with the anterior pituitary like or lutemizing hormone of human pregnancy urine were corroborated by Broad and Berman.¹⁴ We are of the opinion that our results to date warrant further study of the relationship of hormones to peptic ulcer.

*The other three series are similar.

- (c) the urine extract prepared from normal men (32 per cent)
- (d) the anterior pituitary like (lutemizing) hormone of human pregnancy urine (29 per cent)
- (e) enterogastrone (orally), 21 per cent

3 The preparations that resulted in a significant number of animals dying without ulcer are

- (a) the anterior pituitary like (lutemizing) hormone of human pregnancy urine (45 per cent)
- (b) progesterone (33 per cent)
- (c) the anterior pituitary follicle stimulating hormone from pregnant mare's serum (33 per cent)
- (d) the urine extract from normal men (24 per cent) and the urine extract from normal (nonpregnant) women (21 per cent)

The percentage of deaths without ulcer was as high or higher in other series but the results in the latter groups were not considered significant because the average survival time was lower than that of the control series the percentage of animals that lived longer than 135 days was extremely low or zero, and most of the animals that died without ulcer died within 30 days of the Mann-Williamson operation. These apply to the series treated with the posterior pituitary extract plus APL hormone orally administered APL hormone parenterally administered enterogastrone and inactivated APL hormone.

4 Epithelization of the ulcers was noted in a significant number of the animals treated with

- (a) progesterone (80 per cent)
- (b) the anterior pituitary like hormone of human pregnancy urine (38 per cent)
- (c) the heat inactivated APL hormone (38 per cent)
- (d) oral (crude) APL hormone (38 per cent)
- (e) the urine extract of normal (nonpregnant) women (31 per cent)

It is of interest to note that only 8 per cent of the ulcers in the series treated with normal male urine extract showed epithelization similar in per cent of epithelization to that of the untreated animals. It is also important to stress that the per cent of epithelization in another series of Mann-Williamson animals treated with a urine extract prepared from ulcer patients (not included in this report) is also 8 per cent.⁸ In other words the per cent of epithelization is exactly the same (that is 8 per cent) for each of the following three series of animals: the untreated series, the series treated with a urine extract prepared from normal men, and the series treated with a urine extract prepared from ulcer patients. The per cent of epithelization is significantly higher in the series of animals treated with extracts prepared from the urine of pregnant and normal (nonpregnant) women.

In this communication 'per cent ulcers with microscopic healing' (Chart I item 4) includes only those ulcers which showed epithelization at the edges of the ulcers. However, some of the ulcers which failed to show

OSTEOPLASTIC MOBILIZATION OF THE ILIUM

A NEW OPERATIVE APPROACH TO THE INTERIOR OF THE TRUE PELVIS

HANS BRUECKE, M.D., AND HERBERT MOSEF, M.D., GRAZ, STYRIA, AUSTRIA

(From the Surgical Clinic University of Graz Prof. Dr. F. Spath, Chairman)

SURGICAL access to bony lesions situated in the interior of the pelvis has always presented serious difficulties from a technical point of view. In our present paper we propose to exclude from the discussion partial resections of the various parts of the pelvic skeleton, for the removal of localized bone lesions, such as tumors or tuberculous foci.

Our aim has been to develop an operative procedure which would give satisfactory access to the pelvic cavity with minimum trauma to vital structures, good drainage and early functional repair.

The well known incisions sponsored by Bardenheuer, Ollier, Rieder, Tillmanns, Kocher, Roux and, last but not least by Sprengel, give surgical access in varying degree to the outer surface of the pelvis. Sprengel's incision following the iliac crest does to a certain extent allow approach to the iliac fossa and the medial aspect of the hip joint but to attain this end the attachments of the abdominal muscles and the muscle insertions at the anterior superior iliac spine must be severed with all attendant disadvantages. The protruding ilium furthermore presents a serious obstacle to successful management of deep seated bony lesions. Working with the chisel or the burr is difficult and cumbersome especially posteriorly and below the pelvic brim.

Osteoplastic mobilization of a greater or lesser part of the ilium, comprising the major part of the iliac crest and the anterior superior spine leaving the attached muscles intact seemed a logical way of solving the difficulties presented. The access gained is direct and ample, no vital structures are injured, drainage is good and functional repair rapid. The operation is applicable to all localized extraperitoneal and bony lesions below the pelvic brim such as bone abscesses, tuberculosis, foreign bodies and fistulas involving bone. Although the operation would at first sight seem to be a formidable procedure, experience has shown that it is well tolerated and causes comparatively little shock. It is evident that patients should be conscientiously selected and prepared for the operation. An exact anatomic diagnosis should be sought by all available methods such as stereoscopic roentgenograms, radiopaque fillings of fistulas etc.

The operative procedure is best illustrated by Figs. 1 to 3. With the patient lying on his sound side and the operator facing him a curved incision is carried right down to the bone along and slightly below the iliac crest. The anterior end of the incision can be continued past the anterior superior iliac spine down the thigh for about two inches as this will facilitate mobilization of the bone (Fig. 1). The outer aspect of the ilium is then stripped of the gluteal

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Neurohumoral and psychosomatic factors are now generally considered to play an important role in human peptic ulcer. If these factors are associated with the genesis and recurrence of peptic ulcer it is certainly possible that they may operate directly or indirectly through the endocrine glands. Correlated studies of this possibility are desirable.

ADDENDUM

The recent work of Hench¹⁵ indicating the relationship between the pituitary-adrenal complex and rheumatoid arthritis, with clinical improvement following treatment with Compound E is based on the often observed beneficial effects of pregnancy on this condition.¹⁶ This observation parallels our own investigations on the protective effect of pregnancy upon peptic ulcer as summarized in 1939³ and since augmented by numerous experimental and clinical studies. One of us (D. J. S.) thus raised the question whether the beneficial effect of pregnancy on human peptic ulcer might also be due to a pituitary-adrenal mechanism.¹⁷

It is well known that the pituitary is more active during pregnancy and possibly during the active sex life of the female. The pituitary adrenocorticotrophic hormone

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REFERENCES

- 1 Winkelstein, A. Modern Treatment of Peptic Ulcer. New York, 1949. Oxford University Press, p. 23.
- 2 Scotson, F. H. The Treatment and Post Operative Results of Perforated Peptic Ulcers. Brit. Med. J. 2: 680, 1933.
- 3 Saltz, D. J. and Sandweiss, D. J. The Sex Incidence of Peptic Ulcer. Am. J. Surg. 61: 194, 1941.
- 4 Sandweiss, D. J. and Saltz, D. J. The Beneficial Effect of Pregnancy on Human Peptic Ulcer and the Beneficial Effect of the Pituitary-Adrenal Complex on Experimental Ulcers—A Possible Explanation. Harper Hospital Bulletin 7: 1949.
- 5 Hench, P. V. and Scott, W. J. The Beneficial Effect of Pituitary-Adrenal Complex in the Treatment of Rheumatoid Arthritis. J. Clin. Invest. 16: 1, 1937.
- 6 Hench, P. V. and Scott, W. J. The Beneficial Effect of Pituitary-Adrenal Complex in the Treatment of Rheumatoid Arthritis. J. Clin. Invest. 16: 1, 1937.
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- 8 Hench, P. V. and Scott, W. J. The Beneficial Effect of Pituitary-Adrenal Complex in the Treatment of Rheumatoid Arthritis. J. Clin. Invest. 16: 1, 1937.
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- 13 Hench, P. V. and Scott, W. J. The Beneficial Effect of Pituitary-Adrenal Complex in the Treatment of Rheumatoid Arthritis. J. Clin. Invest. 16: 1, 1937.
- 14 Hench, P. V. and Scott, W. J. The Beneficial Effect of Pituitary-Adrenal Complex in the Treatment of Rheumatoid Arthritis. J. Clin. Invest. 16: 1, 1937.
- 15 Hench, P. V. and Scott, W. J. The Beneficial Effect of Pituitary-Adrenal Complex in the Treatment of Rheumatoid Arthritis. J. Clin. Invest. 16: 1, 1937.
- 16 Hench, P. V. and Scott, W. J. The Beneficial Effect of Pituitary-Adrenal Complex in the Treatment of Rheumatoid Arthritis. J. Clin. Invest. 16: 1, 1937.
- 17 Sandweiss, D. J. and Saltz, D. J. The Beneficial Effect of Pregnancy on Human Peptic Ulcer and the Beneficial Effect of the Pituitary-Adrenal Complex on Experimental Ulcers—A Possible Explanation. Harper Hospital Bulletin 7: 1949.

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muscles subperiosteally, to the edge of the great sciatic foramen. The large skin muscle flap thus formed is retracted downward, so that the superior gluteal vessels are exposed (Fig. 2).

The part of the bone mobilized is marked with an *x* in Figs. 2 and 3. Careful experimentation on the cadaver has shown that this should always include the anterior superior iliac spine with the attached sartorius and tensor fasciae latae muscles. A narrow bridge of bone should be left at the great sciatic foramen in order not to break the continuity of the pelvic girdle. Posteriorly it is well to keep clear of the sacroiliac joint and its immediate neighborhood. The cancellous bone in this region is quite thick and the inner periosteum is reinforced by the anterior ligaments of the sacroiliac joint; hence it will be found difficult to mobilize the bone sufficiently if the incision has been carried too far backward. The optimum line for chiseling will be seen in Figs. 2, 3 and 4. Sharp broad chisels of the Lever type or a circular saw can be used for cutting the bone.

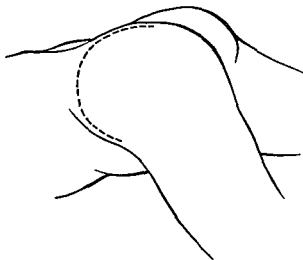


Fig. 1.—Outline of the skin incision for osteoplastic mobilization of the iliopectineal region.

The separated piece with its muscle attachments is pushed medially toward the lower abdominal cavity with considerable force. Subperiosteal stripping of the bone is continued downward on the inside toward the pelvic brim and beyond when necessary. Occasionally (as in Case 3) it may prove more advantageous to displace the mobilized bone upward and outward for better access. A satisfactory approach is thus gained to the anterior aspect of the sacroiliac joint, the medial side of the hip joint, the descending part of the ischium and the horizontal ramus of the pubis. The depth of the wound is crossed by the anterior femoral cutaneous nerve and by the common iliac vessels (Fig. 3).

the mobilized
part of the hip

edily exposed
the common
femoral vessels

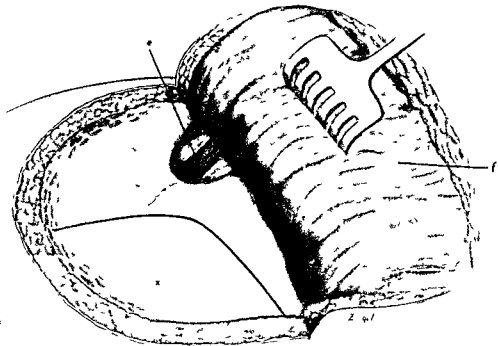


FIG 1 (For legend see opposite page)

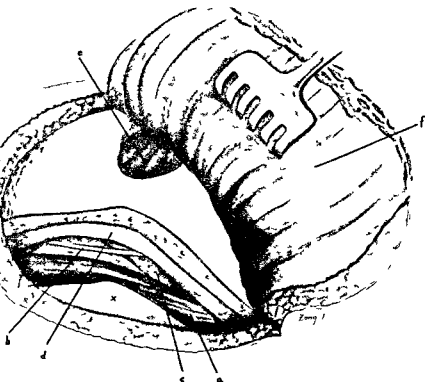


FIG 2 (For legend see opposite page)

At the end of the operation the mobilized part of the bone is replaced and the gluteal muscles are sutured to the iliac crest. Any remaining displacement has proved quite unimportant from a functional point of view, and no attempt need be made to attain perfect alignment by the use of wire sutures. Consolidation will be found sufficient within four weeks and no instability of the hip joint due to muscular insufficiency, has been observed in any case.

Perhaps a few words should be said about the question of drainage. In two of our cases we have been forced to reopen part of the incision to drain an intrapelvic abscess through a trephine hole in the ilium. This experience leads us to advocate immediate drainage through a suitably placed bone opening whenever findings at operation seem to make this desirable (Fig. 4). Four patients have so far been operated upon with very gratifying results.



Fig. 4 (Case 3).—Trauma from roentgenogram after osteoplastic mobilization of the ilium for removal of a piece of shrapnel. Mobilized part of bone held in place by Kirschner wire. The central hole in the bone was made for drainage.

CASE 1.—A 19 year-old soldier had suffered from sciatic pains in the left hip since the age of 15. Movements of the hip joint were limited by pain. The x-ray examination showed narrowing of the joint space and cystic destructive foci in the acetabulum and the descending ischial ramus. All other findings being normal a diagnosis of localized cystic bone disease was made and operation was performed by means of osteoplastic mobilization of the ilium.

The bone foci were found to be caused by tuberculous abscesses. Healing took place smoothly but the later course led to ankylosis of the diseased hip joint.

CASE 2—A 21 year old man had been operated upon one year previously in another hospital. A history could not be obtained, but apparently an opening had been made in the ilium for drainage. The postoperative course had been stormy. When seen by us the patient presented a fistulous opening near the anterior superior iliac spine on the right side. Radiopaque filling revealed a fistulous track entering the pelvic cavity through a hole in the ilium near the anterior part of the spine, and extending backward to the hollow of the sacrum and the great sciatic foramen.

At operation access was gained through osteoplastic mobilization of the hipbone, and the fistula was excised radically by cutting the sacrotuberous ligament. Three months later part of the incision had to be reopened to remove several small sequestra. After this healing was rapid with complete functional recovery.

CASE 3—A 30 year old man in 1943 had received a shrapnel injury in the right lumbar region just below the twelfth rib posteriorly. Several abscesses led to a permanent fistula.



Fig. (Case 4)—Tracing from roentgenogram (preoperative) showing radiopaque filling of fistulous track originating from gunshot injury of right wing of sacrum and of sacroiliac joint.

at the point of entrance. Roentgenogram showed a metallic foreign body 12 by 8 mm. just anterior to the right sacroiliac joint. A radiopaque filling of the fistula led from the external opening below the twelfth rib straight down to this foreign body. At operation the ilium was mobilized as described previously, but the mobilized bone was displaced upward and out instead of being pushed medially into the pelvic cavity. The foreign body was found in the scarred iliacus muscle and removed without difficulty. Drainage was instituted through the external fistula and the bone replaced and held by means of a Kirschner wire. Primary healing took place (Fig 4) and the patient was discharged well fifty-one days after the operation.

CASE 4—A 33-year-old man was wounded by a submachine gun in 1944, the point of entrance being at the left side of the sacrum. He had been operated on several times and the projectile removed. Unfortunately, a case history could not be obtained, owing to war conditions.

When seen by us in January, 1948, the patient complained of a continuous discharge from the right buttock. X-ray examination after filling with iodized oil showed a fistula traversing the buttock, entering the pelvic cavity just above the great sciatic foramen and ending in a round bone defect in the sacrum near the sacroiliac joint (Fig 5).

Surgical approach was by mobilization of the ilium. The fistula was entirely excised. The round bone defect was converted into a flat groove and through and through drainage was instituted. The bone was replaced and the gluteal muscles sutured into place. The postoperative course was complicated by an intrapelvic abscess and a mild osteitis of the wing of the ilium. Drainage was instituted through a large trephine hole and the infection cleared up promptly. After fifty days the patient was up and about and at the time of writing (three months after operation) is practically well.

SUMMARY

A method of surgical approach to the interior of the pelvic cavity is described making use of osteoplastic mobilization of the wing of the ilium. The method gives good access to this difficult field with minimum trauma and no lasting functional impairment. The method is applicable to the treatment of lesions situated at the inner side of any part of the pelvic ring. Four patients thus treated are briefly reported upon.

REFERENCES

- Bruecke H. Die osteoplastische Aufklappung der Beckenschale als Zugangsweg für Operationen an der Innenseite des kleinen Beckens. *Klin. Med.* 1:511, 1946.

TRIGGER FINGER PRODUCED BY EXCESSIVE HEAT

D. ENGEL, M.D., ANDRELL-LYTHAM, LANCASHIRE, ENGLAND

THREE cases of trigger finger are to be described in all of which heat appeared to be the causative factor. Two of the three cases developed by using the same overheated arc welding gun for several months the third followed exposure to Sollux lamp radiation for five minutes. They are of interest from the standpoint of pathology in general and of industrial and preventive medicine in particular. They gain in significance since in a recent Memorandum (1945) by the Factory Department of the Ministry of Labour and National Service the occurrence of trigger finger amongst arc welders was confirmed. 'These were characterised by a locking effect when the fingers were fully flexed and passive resistance was required to obtain full extension which was accompanied by a slight clicking sound. To my knowledge no trigger finger produced by and attributed to heat action has been recorded in the literature.

The trigger finger is a clinical and not a pathologic entity. It is the manifestation of a disproportion between tendon and tendon sheath caused by a stricture of the sheath or by a thickening of the tendon or by both these changes simultaneously. Our knowledge of the etiology of the trigger finger is hazy so much however seems certain that several different causes may lead to the same pathologic result. It is also probable that in some cases the coincidence of at least two factors is necessary for the development of the disease one being the disposition the other the exposition (trauma etc.). The disposition is either local or general. The tendon sheaths of the digital flexor tendons have a natural anatomic stricture opposite the base of the first phalanx. This point is therefore most disposed to further constriction. The general disposition or constitution is more difficult to define. Perhaps the 'arthritic' types of the French are more likely to be affected if exposed to certain irritations. One type of the constitutional trigger finger is more distinct it is the congenital type (Konitschke 1888 Berger 1875) (Cramer and Schleicher described trigger fingers in two uniovular twins.

The commoner form of trigger finger however is the acquired one especially that of traumatic origin (Poulson Tilmann). Rheumatism and gout are two other causative factors mentioned by several authors (Marchesi 1905 etc.). Necker who collected 121 cases from the literature, found that 52 were of rheumatic or gouty origin 13 of traumatic 2 congenital 47 due to occupational strain and 7 of unknown etiology. Necker rejected the trigger finger as an industrial disease. Hauek thought that trigger finger was produced by trauma but he always postulated a special disposition because in his experience the disease was found chiefly in elderly women with arthritic complaints.

Kroh found signs of chronic inflammation of the tendon sheaths in 13 cases on histologic examination. But in his opinion these signs could not be attributed with certainty to an acute or chronic trauma. He does not regard any

at the point of entrance. Roentgenogram showed a metallic foreign body 12 by 8 mm just anterior to the right sacroiliac joint. A radiopaque filling of the fistula led from the external opening below the twelfth rib straight down to this foreign body. At operation the ilium was mobilized as described previously, but the mobilized bone was displaced upward and out in fear of being pushed medially into the pelvic cavity. The foreign body was found in the scarred iliacus muscle and removed without difficulty. Drainage was instituted through the external fistula and the bone replaced and held by means of a Kirschner wire. Primary healing took place (Fig. 4) and the patient was discharged well fifty-one days after the operation.

CASE 4—A 33-year-old man was wounded by a submachine gun in 1944 the point of entrance being at the left side of the sacrum. He had been operated on several times and the projectile removed. Unfortunately a case history could not be obtained, owing to war conditions.

When seen by us in January 1948 the patient complained of a continuous discharge from the right buttock. A roentgen examination after filling with iodized oil showed a fistula traversing the buttock entering the pelvic cavity just above the great sciatic foramen and ending in a round bone defect in the sacrum near the sacroiliac joint (Fig. 5).

Surgical approach was by mobilization of the ilium. The fistula was entirely excised. The round bone defect was converted into a flat groove and through and through drainage was instituted. The bone was replaced and the gluteal muscles sutured into place. The postoperative course was complicated by an intrapelvic abscess and a mild osteitis of the wing of the ilium. Drainage was instituted through a large trephine hole and the infection cleared up promptly. After fifty days the patient was up and about and at the time of writing, (three months after operation) is practically well.

SUMMARY

A method of surgical approach to the interior of the pelvic cavity is described making use of osteoplastic mobilization of the wing of the ilium. The method gives good access to this difficult field with minimum trauma and no lasting functional impairment. The method is applicable to the treatment of lesions situated at the inner side of any part of the pelvic ring. Four patients thus treated are briefly reported upon.

REFERENCE

- Brucke H. Die osteoplastische Aufklappung der Beckenschale als Zugangsweg für Operationen an der Innenseite des kleinen Beckens. Klin. Med. 1: 511, 1946.

TRIGGER FINGER PRODUCED BY PASSIVE HEAT D. INGL, M.D., ANDBELL-LATHAM LANCASHIRE ENGLAND

THREE cases of trigger finger are to be described in all of which heat appeared to be the causative factor. Two of the three cases developed by using the same overheated are welding gun for several months, the third followed exposure to Sollux lamp radiation for five minutes. They are of interest from the standpoint of pathology in general and of industrial and preventive medicine in particular. They gain in significance since in a recent Memorandum (1945) by the Factory Department of the Ministry of Labour and National Service the occurrence of trigger finger amongst arc welders was confirmed. "These were characterised by a locking effect when the fingers were fully flexed and passive assistance was required to obtain full extension which was accompanied by a slight clicking sound." To my knowledge no trigger finger produced by and attributed to heat action has been recorded in the literature.

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The commoner form of trigger finger however is the acquired one, especially that of traumatic origin (Poulson, Filmann). Rheumatism and gout are two other causative factors mentioned by several authors (Marchesi 1905 etc.). Necker who collected 121 cases from the literature found that 52 were of rheumatic or gouty origin, 10 of traumatic, 2 congenital, 47 due to occupational strain and 7 of unknown etiology. Necker rejected the trigger finger as an industrial disease. Hauek thought that trigger finger was produced by trauma but he always postulated a special disposition because in his experience the disease was found chiefly in elderly women with arthritic complaints.

Kroh found signs of chronic inflammation of the tendon sheaths in 13 cases on histologic examination. But in his opinion these signs could not be attributed with certainty to an acute or chronic trauma. He does not regard any

of his cases as being caused by occupational injury. In this respect he follows the great majority of authors who are just as unconvincing as Bertelsmann (1937), who records a self observation. In his surgical work he frequently used bone forceps and eventually developed a right trigger thumb. After an injury of the right arm he used the left hand preferably for bone work and developed consequently a left trigger thumb. Both disappeared after rest. Years later he strained the two small fingers by using a hoe for garden work and developed trigger finger in the two small fingers. In my opinion no more convincing example of an occupational trigger finger could have been adduced.

Rothenberg (1936) refused industrial compensation for a traumatic trigger finger with similarly unconvincing arguments. Only a few of the older authors recognized the occupational factor as being of primary importance. Schulte and Sudeck (1900) described fifteen cases of trigger finger caused by rifle butts in young soldiers. Anteghiano (1886) saw four cases of trigger finger of the right middle finger produced by fencing. Its occurrence in pianists, seamstresses and flutists is also known.

From this short review of the literature it is evident that the trigger finger is not recognized by the majority of authors as an industrial disease and compensation is refused to those affected by it. It is the purpose of this paper to show that, in at least some cases, this view is untenable.

CASE REPORTS

CASE 1—A man aged 33 years had measles, scarlet fever and bronchitis as a child and had been healthy since. Syphilis, gonorrhea, and rheumatism were denied. From 1931 to 1935 he worked as an arc welder. From 1935 to 1941 he did clerical work. He took up arc welding again in August, 1942. In September 1942 his arc welding gun became over heated so that his thumb blistered in spite of the asbestos gloves he was wearing for the work. He used this faulty instrument for six months, six to eleven hours a day. Work had to be interrupted after one half hour to let the tool cool down. (The handle of a normal arc welding gun is covered with rubber and its temperature is not felt through asbestos gloves.)

After having used the faulty tool for six months he noticed in the morning a stiffness of

locke i and could not be opened without effort.

On examination on Dec. 18, 1942 he presented signs of definite trigger finger of the middle and ring fingers; their extension was difficult and was accompanied by an audible click and a visible jerk. Nothing abnormal could be palpated. He was treated for three months with radiant heat and massage but did not improve.

At operation on March 4, 1943 both flexor tendon sheaths were exposed 4 cm proximal and 4 cm distal from the metacarpophalangeal joints. They were found thickened and narrowed, they were slit and partially excised. No pathologic changes of the tendons were seen.

The clicking disappeared after operation but the patient was unable to close the two

— In March 1943 at this time used a normal gun.

In May 1943 the middle
it without the help of the

other hand

By A. M. A. Moore

At the second operation * July 1943 adhesions and regenerated parts of the two tendon sheaths were excised. This operation did not improve the fingers. In September, 1943, the extension of both fingers became restricted and the clicking of the middle finger recurred. Since then the condition remained stationary. Galvanization and diathermy had no beneficial effect.

On examination December, 1943 the operation scar of three inches over the middle finger was adherent to the flexor tendon that over the ring finger was mobile and smooth. The active extension of both fingers in the metacarpophalangeal joints was reduced by 15 degrees. Extension in the other two joints was full. The active flexion of the two end and middle phalanges was reduced by 30 per cent. Passive flexion was possible only against considerable resistance. During flexion of the middle finger a click was audible which could be eliminated by pressing on the flexor tendon over the basal phalanx. The three other fingers were normal. The grip was poor.

December, 1946 the last operation did not improve function. Both fingers were held in semiflexion and could not be extended actively to full extent. The click in both proximal interphalangeal joints was still present. There were vasomotor changes in both fingers.

CASE 2—A man aged 33 years came from a healthy family. He was operated upon for a lung abscess twelve years before admission. He had no complaints afterward. He had no syphilis, no gonorrhea, no rheumatism. From the age of 16 to 20 years he worked as a stationary packer. From 20 to 30 years he did no manual work. From April 1941 to August, 1942 he did arc welding for ten hours a day. From October 1942, he used for four months the same faulty tool as the man described as Case 1. Though he packed the gun handle with a rag the heat penetrated his asbestos gloves and the tool felt uncomfortably hot. He never actually burned his hand. From January 1943, he used another gun.

In March 1943 he felt pain across the right palm during strenuous work. In May, 1943 the right ring and small fingers started locking every morning. Rest improved this condition for six weeks. In June he had a recurrence for a short period, since August, 1943 the complaints became constant.

On examination Sept. 21, 1943, the configuration of the right hand and fingers was normal except for the ring and small fingers being pressed firmly into the palm. The active extension of the two fingers and the middle finger was impossible; the passive extension very painful. After their forced extension function improved but active extension of the small finger was still reduced by 50 per cent and accompanied by a click. There was no muscular atrophy. All movements of the other two fingers and wrist were normal.

At operation in October 1943 incision was made of 8 cm. over the flexor tendons in the region of the first phalanx and head of the metacarpal bones of the third, fourth, and fifth fingers. The three tendon sheaths which appeared thickened and constricted were slit and partially excised in the exposed area. The tendons were normal in appearance and moved freely after liberation. There was a normal course of healing.

In November 1944 the patient had no power in his three fingers and was unable to bend them.

In February 1944, light pentothal anesthesia was given. The patient responded to commands but was unable to bend the three fingers. Manipulation under deeper anesthesia showed adhesions in the incision area. After this manipulation the finger movements improved slightly. The patient did not reappear for re-examination.

CASE 3—This was a man aged 50 years. At the age of 15 years he had suffered from tuberculous coxitis with subsequent ankylosis. Eleven years before admission he had had a right hemiplegia from which he recovered completely. He limped and was unable to walk. He had no other complaints.

left hand for about five minutes. The hand became extremely hot but was not actually burned. Four to five hours after this treatment he felt a stiffness in the left middle finger and could not extend it without effort. Movement was accompanied by a click. A similar condition of the ring finger developed one week later. Both fingers were treated with Sollux lamp for five weeks. They did not improve and remained unchanged afterward.

On examination the man was found to be in relatively good general condition. The right hip was subluxated on account of an old tuberculous coxitis. There were no signs of any active tuberculous process or hemiplegia. The configuration of the left hand and fingers was normal. Nothing abnormal was palpable. The active flexion of all fingers was full and free. The extension of the middle and ring fingers in the metacarpophalangeal joints was also full but in the first interphalangeal joints it was reduced by 50 per cent. This restriction could be corrected only with great effort again: strong resistance with the help of the other hand. It was accompanied by a jerk and click. Extension in the other joints is full.

COMMENT

The three cases described are all typical cases of trigger finger. All three developed after exposure to excessive heat. While in Cases 1 and 2 there was exposure to high temperature over a longer period of six and four months respectively, in Case 3 exposure was only for five minutes. In all three cases the localization of injury was restricted to the area exposed to heat and in all three there was a continuity between trauma and injury. In Cases 1 and 2 the same overheated tool was used under similar circumstances for the same purpose for about the same length of time with the same pathologic result.

In the first two cases no sign of any constitutional disposition could be detected. Both were healthy young men with no history of previous arthritis or local injury. One patient (Case 3) had previously arthritic complaints in his knee but they were due to static conditions in consequence of a tuberculous hip. This patient was a very intelligent and critical man; he was very definite about having had no trouble with his hand previous to its exposure to Sollux lamp radiation and insisted that the complaints started on the day of overheating. This was testified by a witness, a reliable masseur of the hospital who knew the man years before and after the heat incident. A compensation claim did not arise.

Our three cases were observed two years before publication of the Ministry of Labour's *Memorandum on Electric Arc Welding* which described the occurrence of trigger finger amongst arc welders (no figures were mentioned). This Memorandum confirms my opinion that the trigger fingers of the first two patients (Cases 1 and 2) were the direct result of using an arc welding gun and that trigger finger in arc welders thus is an industrial disease. The Memorandum

a fresh one—seems to be the precipitating cause of the disease.

While it is difficult to refute this view, the fact that in my two cases trigger finger developed in two men who used the same faulty tool which differed from other tools only in so far as it became unduly hot makes it more than probable that in some cases at least it is the heat and not the repeated gripping effort which is responsible for this disease. It would be of interest to investigate in the future whether those workers in the arc welding industry who develop

trigger finger used a gun which became hotter than other guns or whether, perhaps these workers were less protected against heat by suitable gloves than those workers whose hands were spared from injury.

If my explanation proves to be correct it will be necessary to watch for trigger fingers in other branches of industry in which overheating occurs. It will be necessary to take more precautions against overheating of tools in general. It will be necessary to watch also whether the different forms of heat treatment like diathermy, short wave diathermy, infrared produce trigger finger when applied over a longer period.

Heat may also prove to be an adequate trauma to produce trigger finger experimentally in animals and thus facilitate the study of this disease so little understood.

The three cases reported are of interest also because they seem to show that trigger finger can develop in healthy individuals irrespective of constitution provided an adequate trauma is applied. It is very unlikely that two healthy young men using the same hot tool should develop the same pathologic condition with the same localization within practically the same period because of a similar faulty constitution and not because of the identity of trauma.

The constitutional factor can naturally never be completely excluded from playing a part in the development of any pathologic condition. Even when a man is killed by a brick falling upon his head his constitution is a contributory factor to his death still one would attribute the death to the trauma. It is the quantitative estimation of the two factors constitution and exposition, which determines whether a disease is considered constitutional or not. As mentioned earlier compensation was refused by other authors to industrial workers who developed trigger finger during their work because their constitution was made more responsible for their injury than their exposure to trauma. It is from the standpoint of the worker's compensation that the question of constitution in relation to trigger finger is not only of academic but also of practical importance.

I consider that in every case of trigger finger in which continuity between a chronic or acute trauma sustained during work (pressure on tendons frequent movements heat) can be proved without evidence of previous localized pathologic changes the worker's right to compensation should be recognized. My observation suggests that in at least some cases trauma is by far the more important factor in producing trigger finger as far as heat is concerned and there is nothing to prove the contrary with regard to other traumas.

I recently saw two further cases which confirm me in this conviction. One concerned a 17 year old girl 20 years of age who did no manual work in civilian life. After using a trowel for planting for several days she developed a typical trigger thumb. The other was a woman 40 years of age who spent over twenty years cutting carpets with large scissors. She also developed a trigger thumb of the right hand. In neither case was there any tangible sign of a constitutional disposition. I considered both cases to be occupational injuries entitled to compensation.

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expresses the tentative view that the very frequent (perhaps 200 to 300 times a day) required to release the spent electrode and insert a fresh one—seems to be the precipitating cause of the trigger finger.

While it is difficult to refute this view, the fact that in my two cases trigger finger developed in two men who used the same faulty tool which differed from other tools only in so far as it became unduly hot makes it more than probable that in some cases at least it is the heat and not the repeated gripping effort which is responsible for this disease. It would be of interest to investigate in the future whether those workers in the arc welding industry who develop

RADIODERMATITIS AND NECROSIS

THOMAS D. CROWN, M.D., AND RAYMOND O. BRAUER, M.D., HOUSTON, TEXAS

IT WOULD be rational to expect that with the advances made in the knowledge of the proper dosage of Roentgen rays burns from this source would become less and less frequent. As a matter of fact, this does not seem to be the case, as in my own practice I am seeing these burns even more frequently than five years ago when I presented a paper on the radical treatment of Roentgen ray burns before the American Surgical Association.¹ These were the opening remarks by Dr. John Staige Davis at a meeting of the Southern Surgical Association in 1925. Now twenty three years later, we feel that much the same statement could be made.

All too often the radiodermatitis or necrosis is the result of treatment of a chronic benign condition especially dermatologic lesions or is the result of negligence or ignorance. Further, we believe that the repeated use of radiation therapy in skin cancers where radiation has failed previously, is a pernicious practice often resulting in an exquisitely painful necrotic wound showing little tendency to heal. In addition, in those cases where the use of radium or x ray therapy is optional or questionable some other form of treatment which does not have the dangerous potentials of radiation therapy is indicated.

The lesions under discussion have been classified into three groups by Porter.²

Group I—Lesions resulting from a single massive dose intentional or otherwise, or a few exposures at short intervals. For example prolonged fluoroscopy forgetting patient during treatment or excessive dosage in treatment of malignancies. There are occasions when a history of exposure to radiation cannot be obtained from the patient. This is illustrated by one of our patients who had what was obviously a radiation ulcer. He was unable to give us any history of exposure. Inquiry of the patient's doctor revealed that repeated fluoroscopic examinations had been carried out for reduction of a fracture while the patient was anesthetized.

Another patient was referred with an exquisitely painful lesion of the back which had resisted all therapeutic attacks for several months including three small x ray treatments. Previous local applications had produced a black adherent eschar which obscured the true nature of the lesion. An early diagnosis of herpes zoster further confused the picture. However at the time of surgical excision the typical pathology of excessive radiation was noted. Detailed questioning finally brought out the history of fluoroscopy of the gastrointestinal tract preceding the onset.

Group II—Patients receiving many exposures over a long period of time in the treatment of various benign conditions such as acne, eczema, psoriasis.

¹Read in part at a meeting of The Texas Surgical Society, San Antonio, Texas, April 5, 1945.

²Received for publication Nov. 15, 1945.

It was suggested by Kroh that there is a similarity between trigger finger and de Quervain's tendovaginitis stenosans. He saw a difference between the two in the fact that while in the latter a chronic repeated trauma is always the causative factor, this is not so in the case of the trigger finger. My observations make the suggested difference between the two syndromes very unlikely. The two are most probably identical clinical entities.

Only two of these cases were treated surgically. As seen, the results of both were very unsatisfactory in great contrast to the excellent results obtained in other cases of trigger finger not produced by heat. A recent paper (Foght Anderson 1947) shows that out of 121 cases of the latter group treated surgically, 119 were cured by the first operation and the other 3 by the second operation. I cannot offer a satisfactory explanation for the bad prognosis of the first group. It is however, possible that the tissue reaction to moderate heat is very protracted and that the fibrosing process goes on long after the irritating factor the heat has ceased similarly to an amine or x-ray cancer which develops years after exposure. If this assumption were correct it might be necessary to operate on these patients in whom the condition was produced by heat at a later period than we did when a further fibrosing process is no longer to be expected. Experience may however, show that these patients should not be treated surgically at all. It may also be wrong to give them Sollux lamp and other heat radiation for treatment.

RÉSUMÉ

Three cases of trigger finger are described. There is circumstantial evidence that they were caused by excessive heat. Two patients handled the same overheated air welding gun; the third had an overdose of infrared radiation.

The recognition of the trigger finger as an industrial disease and the worker's right to compensation under certain circumstances is advocated

Acknowledgment. I wish to thank Mr & M. A. Moore for allowing me to publish one of his cases and Mr Allan for re-examining one of the patients (Case 1) for me.

REFERENCES

- ¹ Antegnato Chor mel d r Ferat et l r Marina Septemler 1866
² Berger Deut he Zt chr f Praet Mel Nr 7 an l 4 18
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atrophic, tight appearance which is particularly noticeable where the contraction occurs over the face. The skin surface is dry, and many telangiectatic vessels can be seen. Keratosis are common, and small to large ulcerations may occur. These usually heal slowly, or eventually not at all. In more advanced cases where the irradiation effect has been deep, all of the tissues may have been reduced to a firm scarred mass usually somewhat depressed below the surrounding surface and present in deeper structures. In such lesions persistent chronic ulcerations are likely to occur. The surface of the



Fig. 1.—This patient received x-ray therapy for a cyst of the tibia. A cancellous bone graft was later required because of a fracture. The flap which would have been entirely satisfactory with normal bones became gangrenous due to impairment of the circulation secondary to the x-ray therapy. The skin outwardly appeared to be normal.

ulcer is usually covered with a yellowish coagulum which may be easily removed, revealing a pale yellowish unhealthy base. Sloughing tissue separates very slowly, often requiring weeks or months. The blood supply of bone is easily damaged by irradiation and may succumb to the slightest infection. Characteristically the dead bone is slow to sequestrate (Fig. 2). Dalmond cited cases of bone remaining exposed and inert for five to seven years.

lupus, plantar warts etc. Extreme caution on the part of the therapist in the treatment of these conditions is indicated. There is a strong temptation to renew the treatment when the lesion recurs and to minimize the latent effect of the previous radiation. Many times the patient is guilty of "shopping around" and unwittingly subjects himself to overtreatment. A very careful history should prevent this.

Group III—Professional roentgenologists

We have had occasion to see 25 patients in Group I, 16 in Group II and 2 in Group III, for a total of 43 with radiodermatitis or necrosis (Table I).^{*} Of the entire group only 7 cases were justified. By that we mean that some other form of treatment would have given equal or better results without the sequelae of excessive irradiation. There were 14 cases of skin cancer in which repeated radiation therapy resulted in necrosis of soft and/or bony tissues, some form of surgery would have been better. There were 14 benign or dermatologic conditions including 6 patients with plantar warts. Prolonged fluoroscopy was the cause in 3 patients.

In the way of prevention the greatest progress has been made in reducing the number of victims in Group III. Present day roentgenologists are well aware of the damage that occurs from frequent exposure and take proper precautions. A big factor in the production of radiodermatitis is the latent period together with the fact that repeated doses have a cumulative effect. The radiotherapist is often unaware of having produced a burn because it may not become evident for months or years or the patient may not return.

TABLE I

	NUMBER OF CASES	
	JUSTIFIED	UNJUSTIFIED
Benign condition		15
Malignant	1	
Malignant but other forms of treatment better		19
Total	7	34

^{*}Two cases in Group III not included in this table

Pathology—Radiation whether from x-ray or radium, is destructive to living tissue. Wolbach^{3b} and others⁴ have described the pathologic findings of excessive irradiation. Briefly the pathology in chronic radiodermatitis consists of hypertrophy of the epithelium atrophy of the corium with loss of the sebaceous glands hair follicles and sweat glands in that order. There is a marked obliterative endarteritis affecting all vessels and seriously reducing the blood supply to the area (Fig 1).

Grossly an area of chronic radiodermatitis has a very typical appearance which is not easily confused with any other condition. The skin has an

L. B. N. N.

Pain is an outstanding feature of all deep burns. It usually does not occur until late except where massive doses have been given in one or several closely spaced treatments in which case ulceration and severe pain may develop within a few days. Porter³ stated that the pain and agony of inflamed x-ray lesions is almost unequaled by any other disease. One of our patients was seen by the psychiatric service to evaluate the pain and the question of narcotic addiction. In chronic radiodermatitis where the radiation has been received in multiple doses over a long period of time itching burning and dryness of the skin are characteristic (Fig. 3).

Chronic radiodermatitis once established tends to get worse with the passage of time. In any event the damaged tissue is a potential source of trouble as it may become necrotic or undergo malignant degeneration at any time. Porter² and Davis¹ both noted that carcinoma was more likely to develop in those patients who had received small repeated doses. This observation has been borne out in the four patients in our series who developed cancer in areas of radiodermatitis. Two were in Group II and two in Group III.

TREATMENT

In regard to the treatment in these cases there is one outstanding fact that should be understood before any treatment is undertaken. Certain irreversible changes have occurred in the tissues resulting in loss of healing and reparative powers and for this reason any treatment which does not involve removal of the diseased area can be palliative in nature only. In our opinion palliative treatment is of value in the following situations: (1) acute ulcerations; (2) for symptomatic relief of the early or mild radiodermatitis; (3) where surgery is refused or otherwise cannot be performed.

For the acute ulcerations moist dressings of saline or boric solutions are helpful. Soothing ointments and lotions are also of value. Many authors speak highly of the value of fresh leaves of the *Aloe vera* plant.⁶ Most patients will require analgesics for relief of pain.

Radon ointment^{7, 11} has been tried by many writers since it was first introduced by Uhlmann¹ and apparently some improvement has been noted in certain cases. We have had no experience with the preparation but a consideration of the destructive and irreversible changes that have taken place in the tissues would seem to offer little hope for real improvement in the process.

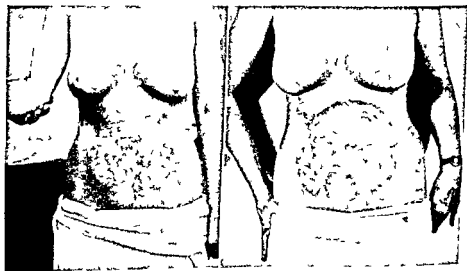
The surgical measures at our command may be listed as follows:

1. Electrodesiccation and coagulation
2. Excision
 - (A) With closure
 - (B) With skin grafting
 - (C) With pedicle grafting
3. Amputation

The simplest surgical procedure is that of electrodesiccation or coagulation. This method is best indicated in the handling of keratotic lesions which are prone to occur in the cases of Groups II and III. It is particularly useful on the hands and face where the keratoses, or early epitheliomas may be co-



Fig. 2.—This patient illustrative of Group II received many radium applications in the treatment of a recurrent basal cell carcinoma. The bone was exposed and inert over a period of four years. An important point to be noted is the futility of drilling holes in heavily irradiated bone for the purpose of producing granulations. Seven patients in this series developed bone necrosis.



A.

B.

Fig. 3.—This patient had received radiation over a period of several years (Group II) for an obscure abdominal condition. She developed itching, burning and pain so that excision and skin graft were required. A split skin graft was possible here because she had not received penetrating rays. A Before B after.

agulated as they appear. It is not advisable to coagulate large areas on the hand, since the resulting scar contracture may limit function.

Excision and closure are indicated whenever possible. Most cases of chronic radiodermatitis are too extensive for simple closure of the wound after excision, and it is here that split skin grafts are indicated. These are suitable on almost any part of the body with the following exceptions. On the plantar surface of the foot this graft is not satisfactory for weight bearing and on the palmar surface of the hand it is subject to contracture. Like wise it may contract when used on large areas on the cheeks and the cosmetic result is poor.

Very large areas may be covered with split skin grafts. As a rule, it is best to apply the graft immediately at the time of excision. There are, however, two situations in which a delay of three to ten days in grafting is indicated. If there is uncontrollable oozing from the wound a graft would not be successful. Where there is a moderate amount of damage to the deeper structures a better take of the graft may sometimes be obtained by permitting granulations to form. Delay in application of the graft may also reveal that the excision has not been radical enough because necrosis may take place in certain areas. A graft which had been placed over such an area would of course be lost.

The pedicle graft is indicated where there has been considerable damage to the deeper structures (Fig. 4). In such cases the tissues are so vascular that a split skin graft would not take. Before surgery one should attempt to evaluate the depth of the damage so that the proper type of coverage can be planned. Knowledge of the amount and type of radiation that has been given is helpful. If the scar is hard, thick, depressed and bound to the deeper structures a pedicle flap will almost certainly be indicated. Ideally, all vascular tissue should be excised completely. In some instances, however, it will be found impossible to carry this out as important structures such as the great vessels may be involved.

Amputation is indicated on the hand when an area of radiodermatitis has become malignant and invaded the deeper structures. It may also be necessary when infection occurs with destruction of tendons, etc.

SUMMARY

1. A plea is made for a greater recognition of the potential dangers of radiation therapy in both benign and malignant conditions.
2. Radiation therapy should be avoided in benign conditions wherever possible, particularly in those that are prone to recur or become chronic.
3. The persistent use of radiation therapy in skin cancers where it has failed initially is condemned.
4. Chronic radiodermatitis and necrosis are essentially surgical problems. Any measures short of extirpation can be palliative only.
5. Split skin grafting is indicated where the damage is essentially superficial.
6. A pedicle graft carrying its own blood supply must be used where damage has involved deeper structures.

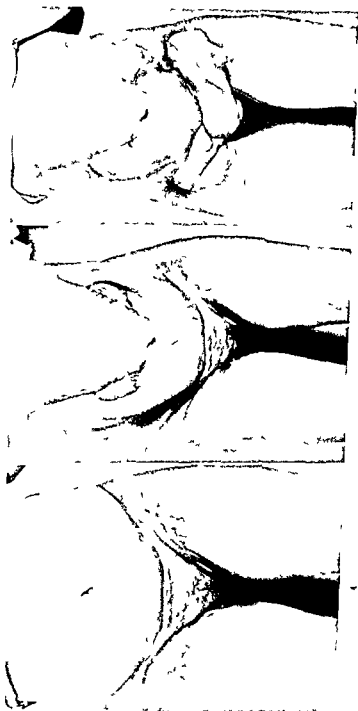


Fig 4. A, B, and C.—This patient was given over 0.000 R X-ray therapy for a carcinoma of the cervix in 1940. She developed a radio dermatitis at both A and B as well as the areas shown in C. The cervical region became extremely painful because of the destruction of the carcinoma. The relief of pain and other

THE LIGAMENT OF TREITZ AS A BARRIER TO INTESTINAL INTUBATION

A CLINICAL AND ANATOMIC STUDY

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(From the Grace Hospital)

THE ligament of Treitz has not received the attention that it deserves as a barrier to intestinal intubation. Surgeons generally are interested only in whether or not the intestinal tube head has passed through the pylorus. If then on the tube is supposed to pass down the gastrointestinal tract without any difficulty. Once the tube head is shown by radiographs to be in the duodenum then the intubation is considered as being successful. Unfortunately in many cases the tube head passes through the pylorus with ease only to become arrested at the distal end of the third portion of the duodenum. It may remain at this location for days with the result that complete intestinal decompression is not obtained.

In studying this problem two important factors were soon found to be responsible for this barrier to an otherwise successful intubation: on the one hand the length of the ligament of Treitz and on the other the weight of the fluid and gas filled loop of jejunum into which the duodenum empties.

That the ligament of Treitz played a very important role in intestinal intubation became increasingly apparent in a study of all patients intubated during the past five years. It should be quite obvious that an intestinal decompression tube whose downward progress was arrested at the duodenojejunal flexure would not be as effective a decompression unit as the tube would be in the ileum. For this reason the importance of any barrier to an otherwise successful intubation must not be minimized.

Anatomists describe the ligament of Treitz as a suspensory muscle of the duodenum. It is described as a bundle of involuntary muscle fibers running from the left pillar of the diaphragm to the duodenojejunal angle.¹ Cunningham² described the ligament of Treitz as a muscular band that springs from the right crus of the diaphragm on both sides of the esophageal opening. It then descends over the left crus behind the celiac plexus, the splenic and left renal veins and the pancreas and then inserts into the duodenojejunal flexure. In children this muscle is well marked and easily isolated and some of its fibers can be traced into the root of the mesentery where they are inserted into the peritoneum. In the adult it becomes ligamentous and loose and is difficult to distinguish from the surrounding fibrous tissue.

The function of the ligament of Treitz is the support of the duodenojejunal flexure. It is thought to prevent this flexure from being dragged downward by the weight of the jejunum. In this fashion it tends to keep the fourth portion of the duodenum at a relatively fixed point.

All anatomists have adequately described the marked variation in the curve of the duodenum as a result of the variation in the position of the third portion

REFERENCES

- 1 Davis J S The Treatment of Deep Roentgen Ray Burns by Excision and Tissue Shifting J A M A 86 1432 1946
- 2 Porter C A The Surgical Treatment of Roentgen Ray Lesions, Am J Roentgenol. 13 31 37, 1925
- 3 (a) Porter, C A The Surgical Treatment of X ray Carcinoma and Other Severe X ray Lesions (Based upon an analysis of 47 cases), J Med. Research 21 331 413, 1909
- (b) Wolback, S B The Pathological Histology of Chronic X ray Dermatitis and Idem
- 4 Lwin, J. J.

TABLE I RESULT

CADAVERS	LENGTH OF LIGAMENT OF TREITZ (IN INCHES)	DIRECTION OF THIRD PART OF DUODENUM
1	2	Horizontal
2	1	Oblique (moderate)
3	1	Oblique (moderate)
4	1	Oblique (moderate)
5	1½	Oblique (acute)
6	1½	Oblique (acute)
7	1½	Oblique (moderate)
8	1½	Oblique (acute)
9	1½	Oblique (acute)
10	1½	Oblique (acute)
11	1	Oblique (moderate)
12	1	Oblique (moderate)
13	1½	Oblique (moderate)
14	1	Oblique (moderate)
15	1	Oblique (acute)
16	1	Oblique (moderate)
17	1½	Oblique (acute)
18	1½	Oblique (acute)
19	1½	Oblique (acute)
20	2	Horizontal
21	2½	Horizontal
22	1	Oblique (moderate)
23	3½	Oblique (acute)
24	3½	Oblique (acute)
25	3½	Oblique (acute)
26	1½	Horizontal
27	1½	Oblique (acute)
28	2½	Horizontal
29	1½	Horizontal
30	1	Oblique (moderate)
31	1½	Oblique (acute)
32	1½	Horizontal
33	1½	Oblique (acute)
34	1	Oblique (moderate)
35	2	Horizontal

In Group 1 a horizontal direction was noted taken by the third portion of the duodenum in its passage from right to left. In these cases the duodenal junction was not acute. In fact in many there did not appear to be any angle at all. In the cadavers in this group were found to have a ligament of Treitz that was fairly long. In all the cases that were dissected out it was found that in this group the ligament of Treitz ranged from one and one half to two and one half inches long. Whenever the ligament of Treitz was found to be two inches long or longer the direction taken by the third portion of the duodenum was invariably horizontal in its passage from right to left. Fig. 1 is a good example of this group. Note that the angle between the duodenum and jejunum is not acute. Figs. 2 and 3 demonstrate clinical cases which could be classified in the same group. Note the direction taken by the intestinal tube in its passage through the third portion of the duodenum. Note also the downward drag of the mercury-containing balloon upon the tube in the jejunum. This type of case is the easiest to intubate and the least likely to impede the downward passage of the intestinal tube.

In Group 2 can be seen a well marked angulation upward of the third portion of the duodenum associated with which there was a rather acute angle at

of the duodenum. The third portion of the duodenum is described as being either nearly horizontal and the fourth part as nearly vertical or the third part may incline upward as it passes to the left and then it would lie in line with the fourth portion of the duodenum.

Because of the clinical observations relative to blockage to intubation at this point it was decided to study anatomically the reason for this.

METHOD

The area of the duodenojejunal flexure was dissected out in thirty five cadavers and the angle between the second, third, and fourth portions of the duodenum noted. In all cases the length of the ligament of Treitz was determined by measuring from its point of attachment to the vertebral column as its upper point and the superior surface of the third portion of the duodenum to which it attaches as its lower point. No attempt was made to measure the length from the esophageal opening or from the left pillar of the diaphragm because that portion of the ligament of Treitz resting upon the vertebral column would constitute a fixed area and would not influence the angulation at the duodenojejunal flexure. It was noted that there was a considerable variation in the obliquity with which the third portion of the duodenum passed from right to left and that this variation in obliquity of the third portion of the duodenum was associated with a concomitant variation in the length of the free portion of the ligament of Treitz. By free portion of the ligament of Treitz is meant that portion of the ligament and its peritoneal fold distal to its attachment to the crura of the diaphragm and vertebral bodies.

Just as the position and type of the stomach seems to be associated with the body build or habitus of the individual so also does the angulation of the third and fourth portions of the duodenum appear to vary with the length of the ligament of Treitz. In individuals with a short ligament of Treitz the third portion of the duodenum was invariably found to angulate upward at an acute angle in its passage from the right to left. The shortness of the ligament of Treitz in this type of individual would result in a rather marked angulation at the duodenojejunal flexure. On the other hand individuals with long ligaments of Treitz presented a third portion of the duodenum almost horizontal in its passage from right to left. In these people the duodenojejunal angle was almost nonexistent since the fourth portion of the duodenum and jejunum lay on almost the same level.

In studying and reviewing the observations in Table I the angulation of the third portion of the duodenum has been classified into three main groups.

1. All cases in which the third portion of the duodenum
whose angle was moderate

the duodenojejunal flexure. In this group the ligament of Treitz was found to range from one half to three quarters inch in length. Fig 4 is an example of this type of case. This cadaver presented a ligament of Treitz one half inch long. Note the acute angle at which the third portion of the duodenum passed from right to left. In this case, the duodenojejunal angle was found to be very acute. It was straightened out in this figure for purposes of photography. Fig 5 demonstrates a clinical example of this group. Note that in this figure the angle at which the third portion of the duodenum passes upward from right to left is so acute that a definite kink is made in the intestinal tube at the junction of the second and third portions of the duodenum. In using intestinal tubes of small luminal diameters such a kink might well occlude the tube at that point. In this patient the intestinal tube did not progress beyond this point for three



Fig 4.—Note very acute upward angulation of the third portion of the duodenum. Ligament of Treitz very short—one half inch.

days. When the patient was ambulatory it was soon noted that further downward progress of the tube was rapid. An examination of Fig 5 suggests that the downward pull of the mercury-containing balloon at the tip of the tube was most efficiently utilized by ambulating the patient. Since making this observation it has been found necessary frequently to ambulate the patient in order to prevent arrest of the tube at the duodenojejunal flexure in this type of case. This was done without any hesitation even in the presence of an ileus due to peritonitis. In fact most of the cases in which this arrest occurred were found as a result of peritonitis.

When it is considered that in such cases the intestinal distention is the result of fluid as well as gas within the bowel and that the proximal jejunum so filled



Fig 1—The horizontal position of the third portion of the duodenum. Angle at the duodenojejunal flexure not acute.



Fig 2



Fig 3

Fig 2—Note the absence of an anastomosis at the duodenojejunal flexure. There is a downward pull of mercury containing balloon tip on intestinal tube.

Fig 3—Horizontal position of the third portion of the duodenum with right angle at the duodenojejunal flexure.

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When it is considered that in such cases the intestinal distention is the result of fluid as well as gas within the bowel and that the proximal jejunum so filled

is heavily weighted it becomes obvious that the downward drag of the weighted jejunum would markedly increase the obliquity of the duodenojejunal flexure. In some cases the downward pull of the proximal jejunum is such that the duodenum is blocked at that point. This is especially likely to occur in paralytic ileus if a short ligament of Treitz results in an acutely angulating third portion of duodenum. Ambulation in such patients, after the tube head has dropped into the jejunum is essential to further downward progress of the tube. Fifteen of the endivers (43 per cent) were found to be in this group.



Fig 5 — Acutely angulated third portion of the duodenum. There is a kink in the intestinal tube at the junction of the second and third portions of the duodenum.

Group 3 consisted of all those cases in which the third portion of the duo-

ment of Treitz was found to be one inch. Fig 6 is an example. Note the angulation of the third portion of the duodenum as well as at the duodenojejunal flexure. Fig 7 demonstrates a clinical case which could be classified in the same group. Here the intestinal decompression tube as it passes through the third portion of the duodenum passes from right to left and upward. The

It will be seen

Fig 8 demon-
the same group

Fig 9 — moderately acute upward obliquity of the third portion of the duodenum

Fig 10 — acute

Fig 11 — acute

angle. This patient was intubated 10 days as a result of diffuse peritonitis. There was tremendous distention



Fig. 6.—The upward angulation of the second portion of duodenum is not so acute as in Fig. 4. Ligament of Treitz is longer.



Fig. 7



Fig. 8

Fig. 7.—Not angulation of the third portion of the duodenum and at the duodenojejunal flexure. All angulations are not acute.

Fig. 8.—The arc at the angle between second and third portions of the duodenum. There is an acute angle at the duodenojejunal flexure, a kink in the intestinal tube at that point, and marked intestinal distention in this case.

In cases of this type the proximal jejunum becomes heavily weighted with fluid as well as gas. The weight of this jejunum causes an acute angulation at the duodenojejunal flexure as noted in this figure. These patients are always difficult to intubate. Ambulation in this patient resulted in a successful passage of the tube beyond the flexure as noted here.

SUMMARY

In a study of all patients intubated during the past five years and an anatomic study of the duodenojejunal flexure of thirty-five cadavers certain fundamental observations could be made. The relationship that exists between the length of the ligament of Treitz and the acuity of the angles formed by the second and third portions of the duodenum as well as between the duodenum and jejunum may be of the greatest importance in insuring a successful intubation in cases of paralytic ileus.

It has been possible to divide all these cases into three groups with respect to the angulation of the third portion of the duodenum. In the first of these groups the direction taken by the third portion of the duodenum in its passage from right to left is horizontal. In this type of case the duodenojejunal flexure is not acute or may even be nonexistent. Such patients are very easily intubated and an arrest of the intestinal decompression tube at the duodenojejunal flexure is never caused. This group was found to constitute 23 per cent of the cadavers dissected. In these cases the ligament of Treitz was found to be long. The length of the ligament of Treitz ranged from two to two and one half inches in all these cases.

In the second of these groups there was a well marked acute angulation of the third portion of the duodenum in its passage from right to left to the duodenojejunal junction. In this group the ligament of Treitz was invariably found to be short, ranging in length from one half to three quarters inch. Invariably in this group the angle formed at the duodenojejunal flexure was found to be so acute that a definite kink could be noted in the intestinal tube. In tubes of small luminal diameter such a kink might well occlude the lumen. Patients in this group were by far the most difficult to intubate beyond the duodenojejunal flexure particularly in cases of paralytic ileus. The downward pull of the heavily weighted proximal jejunum in such cases increased the angulation at the duodenojejunal flexure as almost completely to occlude the bowel. Successful intubation was invariably obtained by turning the patient upon the left side for a period of time to permit the mercury containing balloon tipped tube to run downhill to the duodenojejunal flexure. From that point ambulation was necessary to insure further progress of the tube. In innumerable instances an arrest of the intestinal tube at the duodenojejunal flexure has been demonstrated in this type of case. In all such cases ambulation of the patient was essential for successful intubation. This group constituted 43 per cent of all cadavers dissected.

Group 3 constituted 34 per cent of all cadavers dissected. In this group the angulation of the third portion of the duodenum and the duodenojejunal flexure occupied an intermediary position between Groups 1 and 2. The ligament of Treitz was found to be one inch long. In this group the junction between the

second portion of the duodenum and the third portion was not nearly as acute as in Group 2. The intestinal tube in traversing the duodenum of this type of case showed no tendency to kink. Most of the patients in this group were successfully intubated with ease. Occasionally in a patient suffering from paralytic ileus with a heavily weighted proximal jejunum the angulation at the duodenojejunal flexure was made so acute as to impede the further downward progress of the intestinal tube.

If the patient to be decompressed has little impairment of the propulsive mechanism of the gastrointestinal tract then the angulation at the ligament of Treitz is of little importance. Peristaltic activity in such cases would readily propel any intestinal tube beyond this point. The great importance of a short ligament of Treitz with a concomitant acute angulation at the duodenojejunal flexure is found in cases of atony of the bowel or paralytic ileus in which there is a markedly impaired intestinal motility. In such cases a heavily weighted proximal jejunum pulling upon the short ligament of Treitz could effectively obstruct the intestinal stream. Since it is such cases that need intestinal intubation the most the importance of any method of overcoming this barrier should be evident.

CONCLUSION

1 The ligament of Treitz was found to range from one half inch to two and one half inches long.

2 The length of the ligament of Treitz appeared to be associated with a variation in the angulation of the third portion of the duodenum and the duodenojejunal flexure.

3 Patients with a short ligament of Treitz were found to present a very acute upward angulation of the third portion of the duodenum and an acute angulation at the duodenojejunal flexure. This acute angle often constitutes a barrier to successful intubation.

4 Patients with a long ligament of Treitz present no problem to the intubator as the third portion of the duodenum was found to be horizontal and the duodenojejunal flexure not acute.

5 The angulation at the duodenojejunal flexure in patients with paralytic ileus is of the greatest importance as the downward pull of the weighted proximal loop may obstruct the bowel at that point.

I should like to express my appreciation to Professor Collings of Wayne University for putting at my disposal the anatomic material used.

REFERENCES

1. Horsley C. Human Anatomy Philadelphia 1923 J. B. Lippincott Company, p. 1645.
2. Brahm J. C. and Jamieson F. B. Cunningham. Manual of Practical Anatomy Vol. II New York 1927, Oxford University Press, p. 173.

COMPOUNDS OF ZIRCONIUM FOR X-RAY MEDIA

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IN AN attempt to produce a substance which would render brain tumors radiopaque, many elements and compounds have been investigated in our laboratories. As previous investigators have shown that the electrochemical charge of an ion determines whether or not it crosses the blood-brain barrier, special attention has been paid to this aspect of the compounds used. Broman¹ has shown that under normal conditions only positively charged ions pass through the blood-brain barrier into the brain substance. On the other hand, in the presence of a brain tumor or any local pathologic process the protective mechanism of the blood-brain barrier is altered. This allows the accumulation of negatively charged ions in the involved area.

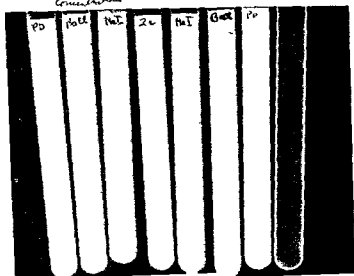
One of the substances investigated, zirconium element number 40 with an atomic weight of 91.2 was found to be relatively nontoxic when injected intraperitoneally in mice and was also found to be more radiopaque than would be suspected. Accordingly, barium, iodine, lead, and zirconium were compared in equal percentage and molar solutions in a series of test tubes. X-ray film in a cardboard holder was used; the radiographic factors were 100 milhamperes, 1 second and 40 kilovolts. The zirconium solution was found to be more opaque than equal amounts of barium or iodine, and approached the opacity of lead (see Fig. 1).

Sodium zirconyl citrate was made after the method of McClinton and Shubert² with the hope that in placing the zirconium in an ionic state the normal blood-brain barrier would not be penetrated but that areas of altered physiology in the brain would permit the zirconium compound to collect and become radiopaque. Thus far we have not been able to demonstrate a brain tumor by x-ray with this technique.

However, when sodium zirconyl citrate was injected intravenously into a rabbit (dosage 7 Gm. per kilogram of body weight) it was noted that the substance was being excreted rapidly by the kidney, and that an x-ray picture of the kidney parenchyma resulted (see Fig. 2). The substance can be found by x-ray examination in the kidneys for one hour after the injection. The radiographic factors were 10 milhamperes seconds and 46 kilovolts. Since impure materials were used in the synthesis of the final product the toxicity necessarily precludes its practical application at the present time.

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the Flora L. Roseblatt and Donald P. and Marian G. Ordway Funds for research in cancer.

Done Sept 29, 1944 few minutes
 2 —————> - moles
 Concentration



64 13570

Fig 1



Fig 2

Fig 1—X ray picture comparing zirconium barium iodine, and lead. The left portion of the picture represents equal concentrations of lead barium and iodine compared with an equal concentration of zirconium. The right portion represents molar solutions of iodine barium and lead compared with an equal molar solution of zirconium.

Fig. —This is an x ray film of a rabbit ten minutes after injecting sodium zirconyl citrate (7 Gm. zirconium per kilo gram body weight of rabbit). Note that the left kidney is partially hidden by the rib cage and spinal column.

The toxicity of the substance was worked out in mice by injecting varying doses intraperitoneally. The lethal dosage for 50 per cent of the mice was 27 Gm per kilogram. However, this toxicity level does not hold true when the injection is made intravenously. The exact level for the lethal dosage for 50 per cent when the chemically pure material is used intravenously has not yet been determined, but it is believed from the experiments already done that it will be in the order of magnitude of one fourth the intraperitoneal lethal dosage per 50.

There are occasions in the management of bowel lesions when the surgeon and radiologist would like to use a radiopaque medium for study but have serious misgivings over employing barium sulfate because of the known tendency of that medium to inspissate in the bowel in partially obstructing lesions. Also there are times when fistulas are suspected and the barium is then withheld due to its deleterious effect when free in the intraperitoneal space. In these situations a solution of zirconium might be used to advantage. Satisfactory x-ray pictures of the dog's gastrointestinal tract have been made with sodium zirconyl citrate, and zirconium oxide. None of the zirconium compounds used were later found in the blood or urine. Practically 100 per cent of the compound was excreted from the bowel in five to six hours.

There is reference in the literature to zirconium oxide being used as an opaque medium but the procedure was patented² by the investigator and there has been no further use made of the method.

At the present time other methods and other zirconium compounds are under study in our laboratories.

Acknowledgment—The zirconium compound used in these experiments were supplied by the Titanium Alloy Manufacturing Division of the National Lead Company.

REFERENCES

1. Brown, Tore. *The Possibilities of the Passage of Substances From the Blood to the*
Surg. Gynec. & Obst. 76:1, 1941.
2. McClure, J. H. *U. S. Pat. 2,111,111* (1938) Zirconium and Thorium.
3. Weiss, J. *U. S. Pat. 2,111,111* (1938) Zirconium and Thorium.

Case Reports

HEMANGIOMA OF THE BREAST

REPORT OF CASE

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HEMANGIOMAS of the breasts are extremely rare. The lesion concerned in this study is of interest because of its location, its rarity, and its failure to respond to radiation therapy. In a series of 5570 breast tumors reviewed by Smythe¹ only 23 hemangiomas were found comprising a percentage of 0.004 per cent. There are two types of breast hemangiomas, the capillary and cavernous. The case reported in this study falls into the latter group. The majority of these tumors are benign although some are malignant. The ratio of those occurring in females to those in males in the study of Smythe¹ was 105 to 1. The majority of the patients were in the 20 to 40 age group. According to Geschickter² mammary hemangiomas are usually of the cavernous type. They are nonencapsulated subcutaneous tumors usually found in the young or middle ages. On palpation the tumors are semis fluctuant and cast a shadow on transillumination. There is one distinguishing feature between this lesion and the intracystic papilloma or papillary carcinoma, namely the absence of a sanguineous discharge from the nipple. For in the former case the vascular spaces are not connected with the mammary ducts. Final diagnosis, however, cannot be made until exploration and study of the tissue are made by microscopic means.

Sherry³ felt that a unilateral tumor of the breast that increases rapidly in size, decreases in volume on compression, only to return rapidly on relaxation which may or may not have a bruit or thrill, all should be suggestive of this lesion. A variety of treatments has been used for these tumors but in reviewing the literature and in the light of our experiences we feel that surgery is indicated. In those cases in which the tumor is small a local excision may be carried out and for the more extensive cases a mastectomy should be done.

REPORT OF CASE

A married white woman aged 33 years was first seen by one of us (C. F. M.) on Jan. 3, 1949, stating that she had a birthmark on the right breast which had enlarged in the past few months. The remainder of her history was essentially negative. She was the mother of two children and stated that the right breast had increased in size out of proportion to the left with each of her two pregnancies.

Physical examination was essentially negative save for a tumor with a small eroded area in the lower involving the upper half of the right breast. It decreased in size on compression and rapidly refilled when the pressure was released. There was no evidence of a bruit or thrill and the tumor transilluminated light poorly. A diagnosis of hemangioma was made and radiation therapy was recommended. Accordingly the patient was referred to a

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*From the San Angelo Medical and Surgical Clinic.

†From the Shannon Memorial Hospital.



Fig 1



Fig 2



Fig 3

×33)

Fig. 3—A higher magnification of a single vessel which shows the effect of the x-ray therapy. About one half of the lumen was obliterated by the intimal proliferation (Hematoxylin and eosin ×100)

roentgenologist who carried out a series of treatments over the next seven months. The patient again reported to one of us (G. F. M.) on Aug. 20, 1948, stating she had had five courses of x-ray therapy without benefit and that it was her feeling that the lesion had progressed. On one occasion, the lesion bled profusely and it was necessary to insert Gelfoam to control this hemorrhage.

Examination on the second visit revealed an increase in the size of the tumor and a large ulcer over the dome. A dry gauze pressure dressing had been applied to control the ooze. There was no evidence of glandular involvement. Mastectomy was recommended. This was carried out on Aug. 23, 1948. At the time of surgery there was no gross evidence of malignancy. The patient's convalescence was uneventful.

The report of the gross and microscopic pathology was made by one of us (L. R. H.) and is as follows:

Gross—The specimen was composed of a breast which measured 15 cm. in its greatest dimension. An ulcer 3 cm. across was present lateral to the nipple. A cut through this ulcer revealed many large caliber blood vessels mixed with fibrous tissue and fat. The largest vessel measured 1 cm. in diameter and was still blood filled. The vascular tumor measured 8 by 7 by 6 cm. in its gross dimensions.

Microscopic—Sections showed a vascular tumor lying under the skin. Starting at the surface a cutaneous ulcer was encountered first. The crater was filled in with necrotic tissue and an exudate made up of numerous lymphocytes and large mononuclear cells and fewer eosinophils. Within 1 mm. of the surface the first large caliber vessels were seen (Fig. 1). Extensive intimal proliferation was noted, and at this superficial level the vessel walls were infiltrated with inflammatory cells similar to those seen in the ulcer crater. The deeper vessels did not show this exudate.

Study of the individual vessels indicated that they were for the most part dilated capillaries. A few of the larger vessels showed scattered muscle fibers but no elastic tissue. The latter vessels were interpreted to be small venules. The typical vascular channel, however, contained blood was lined by a single layer of endothelium, and the rest of the wall was then made up of young connective tissue the result of the intimal proliferation. In some of the smaller vessels complete obliteration had occurred. The endothelial cells showed no evidence of a malignant change.

The supporting stroma was either fibrous or fatty. Near the surface the stroma was infiltrated by numerous lymphocytes and eosinophils. Near the edges of the tumor small capillaries were occasionally encountered which showed a perivascular lymphocyte collar. These capillaries were considered nutrient vessels of the stroma and not a part of the hemangioma. No breast ducts were observed admixed with the tumor.

The overlying skin showed a few changes perhaps due to the x-ray therapy. The cells of the epidermis exhibited pyknosis of nuclei and frequent vacuoles in the cytoplasm. In the immediate subadjacent dermis numerous small capillaries could be seen lined with swollen endothelial cells. Pigment was also increased in amount and was found within chromatophores lying in the dermis.

CONCLUSIONS

1. The diagnosis of a hemangioma is based on the presence of a unilateral tumor of the breast that increases rapidly in size, decreases in size on compression, refilling rapidly on relaxation and which may or may not have a bruit or thrill.

2. Surgical removal is the treatment of choice; local excision for small lesions and mastectomy for the larger ones.

REFERENCES

1. Swarthe E. W. Intramammary Hemangioma. *Ann. Surg.* 115: 71, 1942.
2. Geschickter C. F. Diseases of the Breast, 2nd Edition, Philadelphia, 1940. J. B. Lippincott Company.
3. Sherry Lefroy. Report of a Case of Hemangioma of the Breast, *West. J. Surg.* 42: 319-322, 1934.

INTestinal Lipodystrophy or Whipple's Disease

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WHIPPLE,¹ in 1907, reported a case characterized by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues associated with cachexia and arthritis. This case represented a disease previously undescribed which has since become known as intestinal lipodystrophy or Whipple's disease. No other cases were reported for sixteen years until Blumgart² described three cases in 1923. In the fifteen years that have elapsed since 1923 fifteen cases excluding the one herein described have been reported. The logical explanation for this increased incidence appears to be the dissemination of knowledge about the syndrome among members of the profession. Cases have been reported by Whipple,¹ Blumgart,² Fleischmann,³ Jaicho,⁴ Hill,⁵ Boeck,⁶ Reinhart and Wilson,⁷ Korsch,⁸ Peirse,⁹ Sailer and McGinn,¹⁰ Apperly and Copley,¹¹ Fitzgerald and Kinney,¹² Pemberton, Comfort and Fair,¹³ Rosen and Rosen,¹⁴ Amsterdam and Gryzel,¹⁵ Collins and Berder,¹⁶ and there is a case reported in this paper.

Whipple's case was that of a physician and was characterized clinically by gradual loss of weight and strength stool consisting chiefly of neutral fat and fatty acids being white and creamy, indefinite abdominal pain and a peculiar multiple arthritis. These symptoms and signs are not very characteristic of any particular syndrome but the pathologic findings were unique and Whipple's classical description has not been improved upon to date. The gross changes in the mesenteric lymph nodes were most marked the nodes being very large measuring 3 to 4 cm in diameter and very elastic to the touch. On section they appeared to be a pale yellowish color with virtually total disappearance of lymphatic tissue which was replaced by neutral fat and fatty acids. There was also present a chronic inflammatory reaction associated with many giant cells. The intestinal mucosa showed enlargement of the villi caused by large deposits of neutral fat and fatty acids in the lymph spaces and in infiltration of the glandular tissue by large mononuclear giant cells. The submucosa showed similar changes. The jejunum revealed a pink or red velvety swollen mucosa which was flecked with little pin point yellowish grains that seemed to be intimately connected with the mucosa and in some cases beneath it. Peyer's patches were not conspicuous. The large intestine showed a smooth pale mucosa. The lymphatic tissue of the bronchial glands bone marrow and lungs showed no abnormalities of importance. In our case the villi and crypts of the small intestine showed marked thickening of the mucosa. The mucosa and submucosa contained sheets of foam cells mononucleated and multinucleated giant cells and large clear vacuoles repre-

senting fat droplets. In some areas there was infiltration with polymorphous clear leucocytes. Fat stains with Sudan 4 on formalin fixed tissue showed large and small fat droplet deposits in the foam cells and giant cells.

Since the first case reported by Whipple¹ names other than intestinal lipodystrophy have been applied to the syndrome. Among these are lipophagia granulomatosis, lymphadenocellular mesenteric chyle adenectasis and lymphadenectasis. However from present-day knowledge of the disease the term intestinal lipodystrophy appears to be the most adequate.

CASE REPORT

A 47 year old white man entered Touro Infirmary in January 1934, with a complaint of pain in the arms and ankles. This pain had been present for the past even months and stiffness in both ankle and wrist joints was present. His weight was 163 pounds. Diets of tonics and marked dental caries were noted. The heart was enlarged to the right and an occasional ectopic beat was present. The decayed teeth were extracted and tonsillectomy was done.

In January 1939 the patient again returned to the clinic with a chief complaint of pain in the wrists, ankles, back and cramp in the stomach. This attack had begun three weeks previously when the patient noted a severe cramping pain in the epigastrium. There was much belching and a large amount of gas was passed per rectum. The pain disappeared and reappeared after symptom free periods of three to four hours. It usually began in the epigastrium and radiated to the entire abdomen. It was not related to any particular type of food but did tend to appear three to four hours after meals. At the time of admission the patient was constipated and required either epsom salts or castor oil. The stools were essentially normal in color and consistency. Social history revealed the patient to be a truck driver. He did not use alcohol and smoked occasionally.

In February, 1942 the patient underwent an appendectomy. The recovery was uneventful. He returned to the clinic in April complaining of a low back pain. In orthopedic clinic it was stated that the signs and symptoms were pathognomonic of hypertrophic arthritis of the lumbar spinal spine.

The patient was not seen again until September 1945 when he entered the hospital with a chief complaint of diarrhea and three to seven stools a day for two years. In the interim period of two years, his weight had dropped from 160 pounds to 110 pounds. There was no fever, anorexia, vomiting, jaundice or intolerance to fat or other foods. The stools were brown and showed no evidence of discoloration. X-ray examination of the gastrointestinal tract and lungs while in the hospital at this time were essentially negative. The statement was made in the progress notes that the patient was an emaciated barrel chested man in no acute distress. The skin was slightly jaundiced, swarthy and dry. The tongue was smooth, shiny and red with several darker red macules. The patient was suffering from a hypoproteinemia as well as anemia. In the hospital he was treated with blood transfusions, parenteral vitamin and an adequate diet. The diarrhea continued for some time and then abated.

Some specimens were charged with it was also found that the diarrhea and the shiny red tongue that the patient was suffering from sprue. Gastric analysis revealed a free hydrochloric acid of 6 total acid of 2. Serum protein varied from 4.3 to 5.3 Gm. per 100 cc. Albumin globulin ratio was 2.89 and 2.71. Repeated stool cultures were negative for pathogens of typhoid or dysentery group. The feces were gray and soft and contained no blood parasites or ova. Red blood cells varied between 2.2 million and 3.6 million white cells between 13,000 and 10,000. In November the patient had a bilateral varicose vein ligation with unsuccessful recovery.

The patient returned to the clinic in February 1946 complaining of fourteen pound weight loss. He noted weakness, loss of appetite, nervousness and dyspnea. Gastric analysis

revealed free acid 46, total acid 60. His weight on Oct 19 1946 was 131 pounds. On Dec 7, 1946, the patient had diarrhea for two weeks with three to five bowel movements daily. These were loose and watery. No blood or mucus was noted. Peripheral blood study Dec. 13, 1946 revealed 78 per cent hemoglobin, 38 red blood cells, 1.1 Cm hemoglobin. Re-examination of stools failed to reveal parasites or ova.

He was admitted to the hospital about this time because of a salivary calculus. He was 55 years old. For two months he had a complaint of pain in the epigastrium radiating to the abdomen. The pain was not related to food intake. For three weeks, he had a diarrhea of three to five stools a day. There was no blood or mucus. The face was sunken, the skin was loose and dry. There was loss of skin turgor. The teeth were carious. A hard lobulated mass could be palpated in the submandibular region on the right side at the base of the tongue. Jugular pulsations were visible. Extrasystoles were noted. When the heart was examined a bradycardia of 61 per minute was recorded. The abdomen was believed to be rather large for a person who appeared as emaciated as this patient. Loud borborygmi were heard. Ankle edema was present. Barium enema revealed no organic lesions of the bowel. The diarrhea subsided temporarily following this procedure. It recurred within a few days and repeated stool cultures were negative for pathogenic organisms. On Jan 4 1947, the patient had eleven bowel movements in twenty-four hours. On Jan 6, 1947, proctoscopic examination revealed a smooth inflamed nongranular mucosa. Vitamin therapy was instituted. The diarrhea was believed to be on a deficiency basis. He was given a high carbohydrate, high protein low fat diet. The hemoglobin rose to 12.5 Gm per 100 cc, the serum proteins were 5.11 Gm per 100 cc. He gained 11½ pounds in the hospital. On Jan 13 1947, proctoscopy revealed definite improvement in the appearance of the mucous membrane. The diarrhea was also somewhat improved. On Jan 14 1947 the patient stated he had five bowel movements.

On Jan 16 1947, he had severe cramps. He was very depressed and anorectic. He vomited water frequently but the abdomen was not distended. There was no pain or tenderness and the previously mentioned peristalsis could no longer be heard. On Jan 18 1947, the patient's abdomen was distended. Flat plate showed no fluid levels but there was marked gaseous distention. On Jan 19 1947, under spinal anesthesia a portion of the ileum was found to be gangrenous and was resected. An end-to-end anastomosis was performed. A diffuse peritonitis was noted. Mesenteric thrombosis was the preoperative and postoperative diagnosis. Following operation he developed a gallop rhythm and rapid digitalization was accomplished. On Jan 20 1947, the blood chlorides were 340 mg per cent, CO combining power 57 volume per cent. On the second postoperative day the patient's condition was very poor, temperature 103 F, pulse weak and thready. He was cyanotic and died at 7:50 A.M. on Jan 21 1947.

Gastric analysis revealed free acidity of 18 and a total acidity of 24. The hemoglobin varied from 4 million to 3.6 million, the white blood cells from 6,000 to 13,000, serum proteins varied from 5.11 to 7.49. Repeated stool cultures were negative. Gastrointestinal series at various intervals were not diagnostic of organic disease.

PROTOCOL

General Body Description—This was the body of a fairly well developed and well
- - - white man appearing 57 years of age. There was no discharge from the nose or
throat.

extremities were symmetrical.

Skull and Brain The skull and brain were not examined.

Internal examination The peritoneal cavity contained approximately 1200 cc of a dirty reddish gray exudate. The loops of small intestine were covered with a fibrinopurulent exudate and were distended.

Pleural cavities and lungs There was approximately 20 cc of serous yellow fluid in each pleural cavity. Bilateral apical adhesions were present. The right lung weighed 310 grams. The lower lobe was atelectatic and one section revealed a beefy red surface. The upper and middle lobes were reddish gray, crepitant and one section revealed a moist red surface. No emboli were present in the pulmonary artery or its branches. There was a small amount of mucoid material in the bronchial tree. The left lung weighed 200 grams. The left lower lobe was atelectatic. The upper lobe was similar to that of the right.

Pericardial cavity and heart The pericardial cavity contained 20 cc of yellow fluid. There was definite left ventricular hypertrophy. The heart was opened to reveal a glistening pink endocardium. There was no fibrosis or ulceration of the valves. The coronary arteries were serially sectioned and no thrombus was found. The myocardium presented a reddish brown cut surface showing minute gray scarred areas.

Liver The liver weighed 2100 grams. A fibrinopurulent exudate covered Glisson's capsule. The organ sectioned to reveal a reddish brown surface.

Gall bladder The gall bladder contained approximately 15 cc of dark green tenacious bile. No stones were present.

Spleen The spleen weighed 1260 grams. It presented a soft purplish red trabeculated surface.

Pancreas The pancreas was of normal size and type. It sectioned to reveal a yellow lobulated surface.

Adrenals The adrenals showed a bright yellow cortex and gray medulla.

Kidneys The right kidney weighed 150 grams. Its capsule stripped with ease to reveal a finely granular reddish brown surface. Several cortical retention cysts 2-4 mm in diameter and containing a clear yellow fluid were present. The organ sectioned to reveal a brown medulla. The renal calices and pelvis were not dilated and the ureter was patent. The left kidney weighed 150 grams. The description was similar to that of the right.

Bladder The mucosa showed several focal submucosal hemorrhages.

Prostate The prostate was not enlarged and sectioned to reveal a moist grayish white surface.

Gastrointestinal tract The gastrointestinal tract was removed and opened. The meentery was markedly thickened and edematous. At the time of autopsy no gross enlargement of lymph nodes was noted and therefore no sections of mesenteric nodes were taken. The serosa of the meentery and bowel was covered with friable gray exudate. The bowel was distended up to the anastomotic site which was well closed and showed no evidence of leakage. The remainder of the small bowel was collapsed. The large bowel was slightly distended with gas. The small intestine showed prominent yellow villi that were glomerular. Several superficial mucosal ulcerations were present in the cecum and ascending colon. The appendix was normal.

negative
hemolysis

Microscopic Findings—Sections of adrenals and pancreas showed nothing of pathologic significance. Sections of lung, liver and spleen showed congestion.

Heart There were scattered foci of fibrosis. The myocardial fibers were slightly hypertrophied.

Kidneys There were several retention cysts surrounded by zones of fibrosis containing atrophied tubules. Hyaline glomeruli and infiltrated with chronic inflammatory cells. There were foci of glomerular sclerosis containing atrophied tubules and infiltrated with round cells. Hyaline glomeruli were quite frequent throughout the sections. There were moderate arteriolar changes.

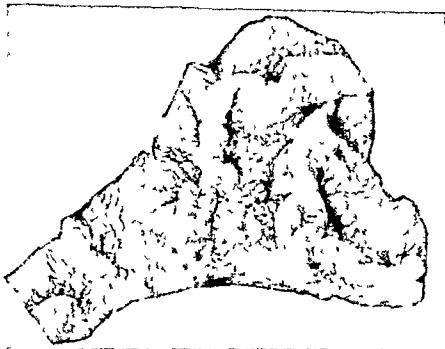


Fig. 1—Segment of upper ileum showing prominent villi of greasy consistency

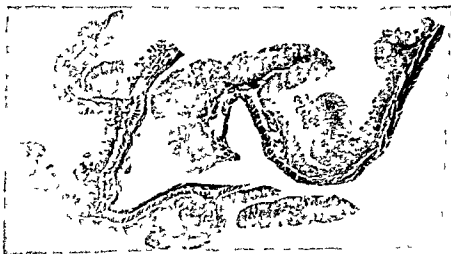


Fig. 2—Micro Summat showing relief outline of enlarged villi



Fig 3—Engorgement of villi with mononucleated and multinucleated foam cells and fat droplets (X100)

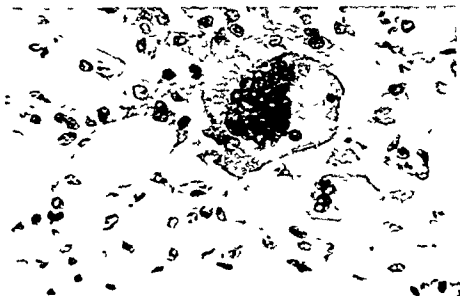


Fig 4—Multinucleated giant cell and foam cell detail (X400)

Gastrointestinal tract Sections of small intestine showed marked hypertrophy of the villi with thickening of the mucosa and submucosa. The villi and crypts were lined with a normal appearing tall columnar epithelium. The mucosa and submucosa contained sheets of foam cells, mononucleated and multinucleated giant cells and large clear vacuoles representing fat droplets. In some areas there was infiltration with polymorphonuclear leukocytes. The muscularis was edematous. The serosa was covered with a fibrinopurulent exudate and there was subserosal edema and infiltration with acute inflammatory cells. Fat stains with sudan IV on formalin fixed tissue showed large and small fat droplet deposits in the foam cells and giant cells. Sections of colon show several foci of mucosal hemorrhage.



Fig 5—Foam cells in submucosa (X100)

Final Anatomic and Microscopic Diagnoses—The diagnoses were (1) intestinal lipodystrophy (Whipple's disease), (2) peritonitis subacute progressive due to (3) *B. coli*, (4) atelectasis bilateral, (5) benign nephrosclerosis, (6) chronic pyelonephritis, (7) retention cysts multiple of kidneys.

SUMMARY OF CASE

The long standing history of undiagnosed diarrhea, abdominal discomfort and anemia along with the gross and microscopic examination make up a typical picture of intestinal lipodystrophy. Death was attributed to a diffuse peritonitis. In retrospect the same intestinal lesions were found in the distal and proximal ends of the infarcted bowel removed at surgery.

COMMENT

With the report of cases since 1923 more data about the clinical aspect of the disease have become available. Males are usually affected from the fortieth to the sixtieth year of life. They generally complain of some vague

gastrointestinal symptoms such as fullness, bloating, and discomfort following the intake of food. Hypotension is usually present. The systolic pressure of the patient reported in this instance was 104. A small percentage developed polyarthritis as our patient did. Other than these symptoms, very few early manifestations occur. The patient is often labeled a psychoneurotic. However, as time passes a fatty diarrhea appears. The stools may be creamy and foamy in appearance, occur four to five times a day, and at times are blood streaked. This blood may be due to minute ulcerations in the small intestine. Later such findings as anemia, wasting, and mild jaundice may be noted. Gastrointestinal series and gall bladder visualization are usually negative. Stool analysis reveals a marked excess of neutral fat and fatty acids. Gastric analysis will frequently show an achlorhydria. A hypocalcemia has been reported in some cases and may cause symptoms of tetany. This finding is especially interesting for hypocalcemia and tetany have been noted in some cases of acute pancreatitis, yet the pancreas at autopsy in intestinal lipodystrophy does not appear to be involved.

The differential diagnosis is most difficult and until 1945 no antemortem diagnosis had been made. Pearse made the first antemortem diagnosis when he removed the mesenteric nodes at an exploratory operation and microscopic examination revealed the true diagnosis. Incidentally this diagnosis was confirmed by Whipple¹ who examined the specimen. The usual diagnoses that had been made previous to autopsy were sprue, Hodgkin's disease, tetany, regional ileitis, colitis, Boeck's sarcoid, and pancreatic insufficiency. The diagnosis is generally made at autopsy as happened in this case.

There has been very little information added concerning the gross pathologic abnormalities described by Whipple¹. The essential pathologic changes occur in the small bowel and in the mesentery. The mucosa of the jejunum and ileum is largely replaced by fat-filled macrophages or foam cells. Whipple¹ stated: "The villi of the small intestine were enlarged by droplets of osmic acid reducing bodies that is neutral fats and fatty acids. Grossly the mucosa is swollen, pink or velvety, and flecked over thickly with pin-point yellowish granules. The mesentery is very thick, feels like rubber, and may be very yellow."

The mesentery on microscopic examination reveals marked dilatation of lymphatic vessels filled with masses of fatty acid crystals. Mingled with the deposits of fatty acid crystals are polynuclear giant cells as well as large mononuclear cells of polyblastic type. The glands per se vary in appearance dependent upon the stage of reaction present. Following the invasion of the fat masses by the giant cells, one can see greater destruction of gland tissue with an invasion of fibroblasts and capillaries resulting in ecchymosis. The giant cells and large mononuclear cells predominate even more and the fat deposits are likewise increased. This process was well described by Pearse² who stated: "The final stage shows a very large giant cell packed with fat deposits of all sizes and shapes and the stroma is made up of dense fibrous tissue full of ecchymoses and giant mononuclear cells."

The lipid chemistry in this disease is interesting. Whipple¹ found 80 per cent of the dry stool in his original case to be fat, 50 per cent was neutral fat and 30 per cent fatty acids. In the lymph nodes the ratio of fatty acids and neutral fat was 15 to 85. Apperly and Copley¹¹ found the same ratio to exist in their case. The total fatty acids, cholesterol and lecithin, are low in the fasting blood and are not increased by a test meal of cream and butter.

Necropsy findings in the various reported cases show a large incidence of fibrous pericarditis seven cases being thus involved. The pancreas in most instances is normal, but has showed a moderate fibrosis in a few cases though never sufficient to even be a suspicious causative factor. Chylous ascites has been found in four cases.

An exploratory laparotomy has been performed in eight cases, namely, by Whipple,¹ Apperly and Copley,¹¹ Amsterdam and Grayzel,¹² Pearse,⁹ and three cases by Pemberton¹³ and in our case. The last case is the only one in which mesenteric thrombosis was present and the only case in which it was necessary to resect the small intestine. Incidentally the same intestinal lesions were found in the distal and proximal ends of the infarcted bowel specimen removed at operation as were found at autopsy in the remainder of the small intestine.

The etiology of intestinal lipodystrophy is most puzzling and several theories have been advanced. Sailer and McGinn¹⁰ stated "The essence of the pathological process appears to be a local necrosis of fat tissue with liberation of lipolytic ferment from the damaged cells." The modus operandi of this necrosis and the nature of the ferment were not revealed. Rokhinsky¹⁷ described a condition in 1885 wherein there was a dilatation of the mesenteric lymph nodes with chyle. Jarcho⁴ believed that dilatation of the lymphatics is the essential characteristic. The obstruction of the thoracic duct is not of much significance as an etiological factor for such a finding has not occurred at autopsy. Again Fauley and Mackie¹⁸ have shown that there is no anatomical evidence of deposition of fat in lymph nodes of cases with thoracic duct obstruction. From the evidence at hand one can surmise that there are no abnormal fats present in Whipple's disease but that an excess of neutral fat and fatty acids is present in the mesenteric intestines and stools. There is no excess of these lipids in the blood stream so it seems reasonable to explore two possible sources of explanation. The first is the possibility of failure by the organ to prepare the fat for absorption. Autopsies in these cases have failed to reveal any pancreatic insufficiency. Blumgart has shown that the lipase content of the intestine is normal and thus further supports the contention that there is no fault of preparation. The remaining source of explanation involves several questions. Is the avenue of absorption into the blood stream at fault? This query appears to hold the answer and was stressed by Ryle¹⁹ and Apperly and Copley¹¹. The following factors appear to show that there is a fault in absorption. (1) Despite the increased fat present in the intestine and mesentery there are low cholesterol, lecithin and total fatty acids in the fasting blood. Furthermore a test meal of cream and butter does not in

crease these values. Reinhart and Wilson⁷ have shown that the dilated lymph channels and lymph nodes of the mesentery are rich in fat content as Whipple¹ originally stated. This also has been stressed by Jarchow⁴ and Ryle.¹² These findings suggest another question which is "Why should the lymphatic lacteals be obstructed?" There is strong experimental evidence by Harris⁸ to show that an acute inflammatory process in interstitial tissue can be aroused by the presence of unsaturated fatty acids with numerous eosinophils being present. Saturated fatty acids cause an inflammatory process with multinucleated giant cells, macrophages and lymphocytes predominating. Thus the inflammatory role played by lipids is a highly suggestive answer to the last possibility. There remains the question "Why are these fatty acids in the lacteals?" Reinhart and Wilson⁷ have attempted to answer this by theorizing that fats are reabsorbed from the intestine in increased amounts. Whipple's disease is a disturbance of the fat metabolism and does not appear to have much surgical significance other than in diagnosis. However in the case herein reported the patient did die of peritonitis resulting from a mesenteric thrombosis. It is the first case of Whipple's disease that has had such a course. The only case reported as cured is that of Pearse.⁹ His patient was placed on bile salts therapy and showed definite improvement with diminution of fat content of the stool. Pearse concluded that the cause of this disease was an abnormal absorption and utilization of fat. He is of the opinion that bile salts therapy corrects this and offers a working basis for the management of the disease. No one is in a position to confirm or deny this hypothesis and it offers the sole therapeutic measure at present.

TABLE I ETIOLOGICAL THEORIES OF WHIPPLE'S DISEASE

AUTHOR	THEORY
Jarchow ⁴	Toxin
Pearse ⁹	
Wright and Copley ¹¹	
Cohn and Loewenheim ¹³	
Hill	
Reinhart and Wilson ⁷	Allergic
Koenigsberg ¹⁰	

a continuing entity

CONCLUSION

The literature on Whipple's disease, a rare disease of fat metabolism involving the small intestine, has been reviewed. Another case has been reported with a most unusual complication, mesenteric thrombosis. The disease offers a problem in diagnosis and the only treatment offered thus far is bile salts therapy. From the maze of conflicting data one can conclude that the multiplicity of theories concerning the etiology of Whipple's disease is sufficient evidence that the etiology is unknown. Whipple's disease should be considered as a possibility in cases of chronic fatty diarrheas.

REFERENCES

- 1 Whipple G H A Hitherto Undescribed Disease Characterized Anatomically by Deposits of Fat and Fatty Acids in the Intestinal and Mesenteric Lymphatic
a
- 2
- 3
- 4
- 5 Hill, J M 1936 Mesenteric Chyladenectasis: Report of a Case Am. J. Path. 13 267
- 6 Boce
- 7 Rein (Intestinal Lipodystrophy)
- 8 Kors Idung im Mesenterium
- 9 Pear 1942 rophy STROPHY 11 906,
- 10 Sailer S, and McGann R J Lipophagic Granulomatosis of the Enteric Tract Am J Digest Dis. 9 55 194
- 11 Apperly F L and Copley E L Whipple's Disease (Lipophagia Granulomatosis),
hy (Whipple's Disease),
intestinal Lipodystrophy
in an Early Stage of the
Whipple Report of a
1947
rophy (Lipophagia Gran
194)
enter Arch Surg 28
- 12 335 1934
- 13 Quoted by Hill
- 14 Fairley N H and Mackie F P The Clinical and Biochemical Syndrome in Lymphadenoma and Allied Diseases Involving the Mesenteric Lymph Glands, Brit M J 1 375 1937
- 15 Ryle, J A Fatty Stools From Obstruction of Lacteal With Note on Coeliac Affection Guy's Hosp Rep 74 1 194
- 16 Haas G M Tissue Reactions to Natural Oils and Fractions Thereof, Arch Path
r Medium An Experimental Study,
- 17
- 18
- 19
- 20
- 21

HUGE CHONDROSARCOMA OF RIB

REPORT OF A CASE

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A CASE of chondrosarcoma of the rib is presented because of its rarity in this location, because of the huge size which it attained, and because of the method employed in closure of the chest defect.

CASE REPORT

The patient was a white woman aged 30 years who complained of a mass under the left breast which had been enlarging for two years. This mass did not bother her until three weeks before admission to this hospital. During the last three weeks she had complained of shortness of breath especially when she leaned forward. She had not previously consulted a doctor.

Eight years previously she had been in a car accident and injured the left side of the chest. At that time there was a moderate amount of pain along the ribs in the left anterior axillary line over the sixth rib but there was no bruise or break in the overlying skin. A few months following the accident she noticed that a small hard mass measuring about $\frac{1}{2}$ inch in diameter and height was attached to the sixth rib along the left anterior axillary line. This small mass along the rib started to enlarge two years before admission, and it grew steadily to its present huge size. She noticed no cough. Appetite and general condition were excellent.

On examination the patient was found to be well developed and well nourished. The breast was displaced anteriorly and medially by a large tumor mass which measured 20 by 25 cm. The tumor extended from the midaxillary line to within 3 cm. of the sternum and it extended up to the fourth rib and down to the seventh rib (Fig. 1). The mass was as firm as the adjacent ribs and seemed to be part of the ribs. It was nodular and there was limited motion between the tumor and the overlying skin. The chest appeared to have no mediastinal shift and respirations were heard equally on both sides. The heart was normal. Blood pressure was 110/84.

Röntgenograms of the chest showed a very large soft tissue shadow on the anterior lateral portion of the left lower part of the chest. The central portion of this soft tissue mass contained a large amount of dense irregular calcific material (Fig. 2). A diagnosis of chondrosarcoma was made and it was thought that the lesion had arisen from the lateral portion of the left sixth rib.

Since the tumor seemed well delimited the decision was made to excise it. The anesthetic was intratracheal cyclopropane.

Two curved incisions were made from the head of the humerus to the costal margin including an elliptical segment of skin 22 by 9 cm. The breast was also included because at this time it could not be determined whether the tumor involved breast tissue. Skin and subcutaneous tissue were easily dissected from the tumor both medially and laterally.

It was found that the fifth, sixth and seventh ribs were incorporated in the tumor. Thirty centimeters of these ribs were resected going 2 cm. medially and 4 cm. laterally to the tumor. There was a layer of tumor between the pleura and the ribs 4 to 6 cm. in thickness. A block dissection was made including ribs with attached tumor, muscles, soft tissues and pleura. No adhesions between the lung and the tumor were noted. There was however a 3 mm. pearly white nodule on the surface of the lung near the lower margin of the upper lobe. This nodule was excised including a little lung tissue about it.

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A 30 by 14 cm defect in the chest wall was closed by a graft of fascia lata. Over this was placed a pedicle graft from the anterior portion of the latissimus dorsi muscle. The pedicle was left attached superiorly to preserve its nerve and blood supply. A Foley catheter was inserted into the pleural cavity through a stab wound below the incision. A Penrose drain was inserted between the muscle graft and the subcutaneous tissue. The skin was closed with continuous silk suture.

Pathologic Report (Mrs S. Uny, Ill. p. No. 91003)—The tumor mass measured 30 by 25 by 14 cm and weighed 2940 Gm. One surface was covered by an elliptical segment of skin measuring 20 by 6 cm. This had a nipple and an areola near one margin. The underlying breast tissue was well defined from the underlying nodular mass and was normal in appearance.



Fig. 1—Preoperative photograph showing the huge size of the chondro sarcoma involving the fifth and sixth rib.

The mass of firm tissue was irregularly lobulated. The cut ends of three ribs protruded on opposite margins. Section across the mass showed pearly white translucent tissue which centrally became more yellow less firm and somewhat more opaque. There were numerous small cavities ranging from 0.5 to 3 mm in diameter. The cystic spaces were filled with a lightly yellow clear viscid fluid. Centrally in the position of the middle member of the three ribs included was an irregularly shaped area of bone formation measuring 6 by 3½ by 2 cm. This bone contained red marrow. The upper of the three ribs showed slight irregularity of its periosteal surface. The lower rib was not involved in this tumor mass.

There was also a 5 mm nodule of tissue which was solid and pearly white embedded in lung parenchyma.

Microscopic—The cartilage part of the tumor was highly cellular with large plump cells (Fig. 3). Multinucleated cells were common and multiple cells were present in many

lacunae. There was little evidence of regular orientation of cells (Fig. 4). Sections of the bony areas showed a layer of fibrous tissue interposed between the bone and cartilage so that the two tissues were not intimately intermingled. Section of tumor made from the lung showed a highly cellular cartilage with considerable variation in size of cells and frequently more than one cell was present per lacuna. Multinucleated cells were not apparent. There is no apparent order in arrangement of cells.

Diagnosis.—The diagnosis was chondrosarcoma of the fifth and sixth rib.



Fig. 2.—Fluorogram of the chest showed a very large soft tissue shadow on the anterior lateral portion of the left lower chest. The central portion of this soft tissue mass contained a large amount of dense irregular calcific material.

Postoperative Course.—Postoperatively the patient was given oxygen intranasally and penicillin intramuscularly. Continuous suction was applied to the catheter placed in the pleural cavity. She had a temperature reaching 101° F for six days and 100° F for six more days. One hundred twenty cubic centimeters of serosanguineous fluid were aspirated from the pleural cavity on the fourth postoperative day. She had a surprisingly tranquil convalescence and complained more of pain in the thigh at the donor site of fascial lata than of discomfort of the chest.

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To offer some protection to the rib defect, a kidney shaped aluminum plate was designed and fitted to the curvature of the chest wall. She wears this for protection only when she may be in a crowd (Fig. 5).

FIG. 3



Fig. 4

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Since no apparent tumor remained, and because of the radioresistance of cartilaginous tumor, no deep roentgen therapy was given.

This patient was seen three months after operation, and there was no evidence of local recurrence. General health was excellent and she was able to carry on all her usual activities.



Fig. 5—Intraoperative photograph showing the location of the incision and the protecting metal shield.

DISCUSSION

Chondrosarcomas of the ribs that have been reported were usually small.^{2,3} One other large tumor was presented by Harper.¹ This tumor followed trauma. It grew slowly for six years then it enlarged greatly.

In Harper's case and in this case a small nodule was present for several years before rapid growth began. One can only speculate as to whether this represents disturbed healing of a rib fracture or whether injury in the area called attention to a pre-existing nodule perhaps an osteochondroma attached to the rib.

Since doing this operation we find that Mayer⁴ had also used fascia lata to close a similar operative defect. We have been unable to find any record of a case in which latissimus dorsi muscle was used as a pedicle graft to help close a defect in the chest wall. Firmness was obtained by the fascia lata and

increased protection, thickness, elasticity, and movability for the skin by the latissimus dorsi muscle graft.

CONCLUSIONS

1. A case of huge chondrosarcoma arising from the left sixth rib and extending to the fifth and seventh ribs has been presented.

2 There was a history of trauma followed by slow growth for six years, and then rapid growth to an enormous size in two years.

3 A large operative defect in the chest wall was repaired by fascia lata and a pedicle graft of latissimus dorsi muscle with excellent functional results

REFERENCES

- | | | | | | |
|---|---------------|--|---|--|------------------------------------|
| 1 | Harper F | | | | 11 ^a , 194 ^d |
| 2 | Harper, F | | | | 13 ^b , 197 ^b |
| 3 | James, R M | | | | |
| 4 | Mayer L | | | | |
| 5 | Lichtenstein, | | I | | 19 57 ^c , |
| | 1943 | | | | |

Editorial

The Quest for a 'Blood' Substitute

DURING the last ten years much effort has been devoted to find the elixir that is epitomized by the term "blood substitute". By its very definition, a substitute should have all or many of the attributes of the material which it is to replace. A moment's reflection will prove that there is no substitute for blood. The term "blood substitute" is a misnomer. It can denote only the particular properties that the individual defining the term may have in mind.

If we remove the attributes of the red blood cell and of the other formed elements from our considerations we are limiting our search to a material that can replace the known and suspected functions of plasma. These functions may be defined briefly as: (a) maintenance and stabilization of the blood (plasma) volume, (b) transport of hormones between tissues, (c) transport and mobilization of antibodies, (d) protection against blood loss by components of the clotting mechanism, (e) transport of lipids and other substances closely associated with the plasma proteins, and (f) the nutritive functions of the plasma proteins.

A complete plasma substitute should attempt to fulfill the attributes just listed. Here again a moment's reflection will convince one that the only substitute for plasma would be plasma itself. From the practical and economic point of view the supply of this natural substitute cannot meet the potential needs for such a replacement solution.

Therefore our definition must be further delimited to encompass those qualities that are needed to the greatest degree. What we are seeking predominantly is a material that first will maintain and stabilize the blood volume in those situations where this is of greatest importance, and that, second, may have nutritive properties. It is too much to ask of any material that it also furnish hormones, antibodies, etc. Accordingly, our philosopher's stone should be sought in the name of a plasma colloid substitute.

What are the requirements that such a substance should have? Some of these may be listed. It should have an acceptable molecular size that will make it an active plasma colloid. It should be retained in the blood stream for a suitable period of time. It should be nontoxic and not be deposited in the tissues. If excreted as such it should not cause nephrotoxic changes. It should be disposed of by the body by common metabolic pathways which would imply that its structural units and chemical linkages can be attacked and hydrolyzed by the enzymes of the tissues.

Let us consider some of the materials that have been proposed and investigated under the heading of "blood substitute" but more accurately defined as a plasma colloid. Gum acacia and pectins have been investigated. True, they do have the requisite colloid osmotic effect, but nature did not endow the

increased protection, thickness, elasticity, and movability for the skin by the latissimus dorsi muscle graft

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REFERENCES

- 1 Harper, F. D. Surg 11 446 194
- 2 Harper, F. Surg 9 13 194
- 3 James, R. M.
- 4 Mayer, L. J Path 19 43
- 5 Lichtenstein, 1943

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK M.D.

EXPERIMENTAL EMBOLISM OF THE PULMONARY ARTERIOLES AND CAPILLARIES

(FORFID) I (RIFIN, JR. M.D. * AND HIPAM F. I (SSEN, PH.D. †
ROCHESTER, MINN.

THERE have been numerous investigations concerning the mechanism of death in pulmonary embolism. Likewise there have been many attempts to reproduce in animals the different types of pulmonary embolism seen in human patients. Churchill¹ classified the types of fatal pulmonary emboli as (1) complete obstruction with immediate death (2) partial obstruction with delayed death which he attributed to reduced effective blood volume causing a diminished cardiac output with falling blood pressure and rising venous pressure and (3) partial obstruction with delayed death in which there was a component of failure of the right side of the heart. Katz classified pulmonary emboli into (1) the large snarl-like embolus which occludes the bifurcation or plus either main branch of the pulmonary artery (2) the emboli of intermediate size which occur in showers and plug smaller pulmonary arteries and (3) the more minute emboli occurring in showers which plug the arterioles. This last classification reflects the methods used by various investigators, for a partial survey of the field shows that emboli have been produced in (1) the pulmonary artery or either of its main branches^{2, 3, 4} (2) the smaller pulmonary arteries^{5, 6, 7, 8, 9, 10, 11} or (3) the arterioles and capillaries.^{12, 13, 14, 15}

Emboli of the last type that of the arterioles and capillaries have excited much interest because of the apparent disproportion between the amount of lung tissue affected and the symptoms produced. This has resulted in the use of suspensions of starch or barium sulfate as agents in attempts to reproduce this phenomenon in animals.

HISTORICAL REVIEW

As far as can be determined from the literature Dunn² was the first in this country to use starch in experimental pulmonary embolism. He found that injecting 40 to 75 cc. of a 1:4 potato starch suspension into the jugular vein or right ventricle of goats weighing 18 to 19 kilograms caused a great rise in venous pressure a fall in systemic blood pressure and death in five to thirty minutes with respiratory failure occurring before the heart stopped beating. Microscopic examination of the lungs of these animals showed all pulmonary arterioles up to 2 mm. in diameter filled with starch granules. He did not mention the size of these granules.

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animal body with enzymes capable of hydrolyzing these pentosans. Consequently they were found to be deposited in the tissues to a greater or lesser degree, with deleterious results. A material so foreign to our body economy does not fulfill the second major requirement, namely, that of being utilized. Polyvinyl pyrrolidine, polyvinyl alcohol and methyl cellulose are also completely foreign to the body.

Two materials, dextran and gelatin, having colloidal osmotic activity have also been investigated. Both are composed of simpler units natural to the body. The former is composed of D-glucose predominantly in 1-6 α glucoside linkage. It is derived from a bacterial polysaccharide which has been hydrolyzed to a molecular weight of around 100,000. The latter is a derived protein prepared from collagen by chemical treatment. It is composed of L-amino acids linked together by peptide bonds. Both its constituent amino acids and manner of linkage are entirely natural to the body. Both should furnish metabolizable energy if they are hydrolyzed completely within the body.

In a recent editorial in the *Journal of the American Medical Association* (139:850, 1949) 'Dextran as a Plasma Substitute' a comparison is made of Dextran, the plasma proteins and gelatin. It is with these comparisons that a further word of clarification is necessary. Distinctions are drawn which are not as clear cut as they are reported to be. Neither Dextran nor gelatin has the globular form in their molecular dimensions which is found in serum albumin. This disparity of molecular parameters has much to do with the fact that approximately 25 per cent of Dextran and 50 per cent of gelatin injected intravenously are excreted through the kidneys in their original form. Both substances must be partially hydrolyzed by chemical means before they are useful as plasma colloid substitutes. This reduction in molecular size which is thereby achieved increases the osmotic activity of the preparations and reduces the likelihood of pathologic storage of the original macromolecules. Both of these substances are composed of substances entirely native to the body and nothing so far reported significantly demonstrates the superior value of Dextran over gelatin in this regard.

There has been far too much loose talk and poor writing on this subject. The factors which will determine the relative value of these two substitutes will reside in other physical attributes of the materials, their relative ease of preparation and the safety of their parenteral administration.

—I S Ravidin

arterioles and walls of the alveoli. They did not report examining the heart or brain microscopically. In these experiments an anticoagulant was not used.

These authors concluded that pulmonary hypertension proximal to an obstructing pulmonary embolus is the essential cause of death and is responsible for the electrocardiographic changes. It is their opinion that the pulmonary visoreceptors both vagal and sympathetic, are highly sensitive and that they are capable of producing such widespread changes as vasoconstriction in the pulmonary vascular bed, a fall in blood pressure, vagal inhibition of the heart, coronary constriction and bronchial spasm. Thus they feel that certain neurocirculatory changes are the major contributory causes of death in smaller pulmonary emboli which, by virtue of the minor amount of pulmonary tissue devitalized, should not cause death.

Jesser and de Takats⁴ reported that vagal mediated reflex bronchoconstriction and bronchosecretion were induced experimentally by pulmonary embolism and that in human beings these responses are some of the major causes of postoperative pulmonary atelectasis.

Megibow, Katz and Steinitz² studied the three forms of emboli, using the massive emboli method of Mendlowitz¹² and using pea seeds for embolization of smaller arteries and a 1:20 starch suspension for embolization of the arterioles and capillaries after the method of Binger, Brow and Branch.¹⁰ They found in their studies of starch embolization of dogs that the elevation of pulmonary arterial pressure could be integrated with increased pulmonary arteriolar resistance resulting from the mechanical obstruction by the starch granules in the arterioles since repeated dosage of the suspension produced further increments of pressure elevation. They expressed the belief that the cause of death is the embolus in the pulmonary arterial tree, acting as a direct mechanical deterrent to the flow of blood through the lungs.

Megibow, Katz and Feinstein¹¹ studied the kinetics of respiration in pulmonary embolism using a 1:20 suspension of starch in dogs. They showed in experiments with massive emboli that distention of the great veins particularly the mouth of the superior vena cava by pulmonary hypertension caused tachypnea and dyspnea which in turn could be eliminated by bilateral cervical vagotomy. In embolization with starch they postulated that the cause of the tachypnea was a reflex arising from distention of the smaller pulmonary arteries by starch and they explained the absence of dyspnea in this type of embolism by suggesting that this reflex overpowered that arising from distention of the great veins. Bilateral cervical vagotomy in these experiments decreased but did not eliminate the tachypnea. They did not use heparin in their experiments and microscopic examination showed antemortem clots around the starch granules.

Kinney, Haynes and Dexter¹³ described a new method of producing pulmonary embolism. A Courmand catheter was introduced into the external jugular vein and passed under roentgenoscopy to either branch or a smaller ramification of the pulmonary artery. Haynes, Kinney, Hellems and Dexter¹⁴ placed a balloon on the end of a venous catheter which was inserted into a

In a second series of goats he found that lesser doses of the starch suspension produced death in one to eight hours there being a gradual downward progression during this period. Dunn showed that in this type of pulmonary embolic death there is a normal percentage of saturation with oxygen of the arterial and venous systems after embolization and also that the carbon dioxide content in arterial blood was essentially unchanged by embolism. He found that the tachypnea induced by moderate doses could be prevented or eliminated by bilateral cervical vagotomy. His conclusion was that the tachypnea was caused by spasm of the bronchial musculature. Regrettably he did not state what influence, if any, the vagotomy had on the lethal effect of the emboli. It is important to note that he did not find starch granules in the cerebral or renal vessels and expressed the belief that his experimental findings were not the result of the presence of starch in organs other than the lungs.

Binger, Brow, and Branch²² repeated the procedures of Dunn using in dogs a 1:20 suspension of potato starch in saline solution. They also showed the influence of the vagi on the tachypnea when they prevented or eliminated it by freezing both vagi and went further to show that the tachypnea of an oxygen want or of a carbon dioxide excess was similarly affected by freezing both vagi.

The starch granules used in their experiments ranged from 5 to 60 microns, averaging 20 to 40 microns. They reported that starch could not be found in any organ except the lungs and that in the lungs it was lodged in the arterioles and capillaries of all lobes, being predominantly in the arterioles. They suggested that the effect of starch is not of an irritative nature as shown by results of the gradual infusion of the starch suspension into an animal. An effect was not seen until a certain amount of starch had been given and then the effect was dramatic.

Villaret, Justin Besançon, and Bardin²³ noted that sectioning the vagi of rabbits increased seven times the amount of powdered pumice stone necessary to produce sudden death. After sectioning the cervicothoracic sympathetics they reported that one fourth of the previously fatal amount injected was lethal. They also showed that epinephrine and atropine in combination could delay sudden death. These workers suggested that sudden death was due in part to reflex sympathetic inhibition. Shock was considered by them to be the manifestation of the inhibition.

De Takats, Beck, and Fenn²⁴ injected an 8:17 suspension of potato starch in water into the ear veins of thirty-five rabbits and found that 2 c.c. was the minimal lethal dose causing dyspnea, cyanosis, convulsions and death in every animal in five minutes. One and one-half cubic centimeters of the suspension killed 30 per cent of the animals injected. 1 c.c. killed none. Sublethal doses were found to cause dyspnea, cyanosis, restlessness, micturition and defecation but within one-half hour the respiration, pulse, and color of the animals were normal. Microscopic examination of the lungs showed the starch granules ranging from 50 to 150 microns in size in the lobular arteries.

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These authors concluded that pulmonary hypertension proximal to an obstructing pulmonary embolus is the essential cause of death and is responsible for the electrocardiographic changes. It is their opinion that the pulmonary vasoreceptors, both vagal and sympathetic, are highly sensitive and that they are capable of producing such widespread changes as vasoconstriction in the pulmonary vascular bed, a fall in blood pressure, vagal inhibition of the heart, coronary constriction, and bronchial spasm. Thus they feel that certain neurocirculatory changes are the major contributory causes of death in smaller pulmonary emboli which, by virtue of the minor amount of pulmonary tissue devitalized, should not cause death.

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lobar pulmonary artery. The balloon was then dilated by a pressure higher than that in the pulmonary artery so as to obstruct the blood flow to that lobe. The obstruction and distention of the lobar pulmonary artery in this manner did not produce a constant change in the respiratory rate, pressure in the femoral and pulmonary arteries, or heart rate of anesthetized and unanesthetized dogs. In contrast, they stated precapillary emboli produced by the slow infusion of a 1 per cent suspension of *Lycopodium* spores measuring 20 to 30 microns in diameter into a lobar pulmonary artery in anesthetized animals regularly produced an increase in respiratory rate, pulmonary arterial and right ventricular pressure, electrocardiographic changes, and a decrease in femoral arterial pressure, leading to death if the infusion was continued. There was a progressive fall in the cardiac output and only terminally was there a significant rise in peripheral venous pressure. The circulatory changes accompanying embolism were not abolished by vagus section and pulling of the spinal cord.

Binet and Burstein¹⁸ reported using a suspension of *Lycopodium* powder in petroleum oil or barium sulfate in water as pulmonary embolic agents in dogs. They concluded that the hypertension of the lesser circulation is caused by a local reflex spasm of the pulmonary arterioles initiated by mechanical endovascular irritation by the embolizing particles and some peripheral reflex by excitation of the vagus, as well as the mechanical obstruction of the pulmonary arterial tree. Conversely they concluded that the hypotension of the greater circulation is not a reflex but results from the mechanical obstruction of the blood in the lungs, which prevents its return to the systemic arterial tree. They felt that the mechanical obstruction of the pulmonary circulation by the emboli was insufficient to explain the pressure changes which occurred in the pulmonary artery. In their opinion this could be explained by an intense spasm of the pulmonary arterioles in addition to the mechanical obstruction. They found that during the embolism a peripheral vasoconstriction existed because of the diminution in the cardiac output.

Smith and Hura¹ in a recent preliminary report stated that in anesthetized heparinized dogs with open thoraces fine methril or ureteral catheters were introduced into the right ventricle or the main pulmonary artery through a small stab incision and guided to any lobar arterial branch. Suspensions of starch or barium sulfate, both found equally effective, were then introduced into the artery in selected doses in such a way as to prevent retrograde flow of the material. The dogs died two to three minutes after the injection. However, when such agents as fine glass beads, poppy seeds, or *Lycopodium* spores were injected there were no significant effects. Since embolic particles such as beads or *Lycopodium* spores did not produce circulatory dynamic changes and finer materials produced severe circulatory changes, they reasoned that pulmonary "capillary" emboli affecting a restricted portion of the pulmonary vascular bed may cause death apparently from pulmonary vasospasm and circulatory failure.

Because of the equal effectiveness of starch or barium sulfate in their experiments, they preferred to use barium sulfate most often in a 5:4 sus-

suspension because of the ease with which it was injected as compared to a 1:1 starch suspension. In dogs weighing 10 to 15 kilograms 2 to 3 cc was the usual dose injected slowly over a period of twenty to thirty seconds. Occasionally a 14 inch (about 0.6 cm) Penrose drain tubing or a wide rubber band was placed around the artery containing the catheter. In such instances the lethal effect was obtained after injection of the embolic material only by releasing the ligature.

Holden Shaw, Cameron Shea and Davis⁸ reported not finding any evidence to support the supposition that pulmonopulmonary, pulmonocoronary or pulmonovascular depressor reflexes contribute to the death of dogs after massive pulmonary embolism. Cervical vagotomy was performed on eight dogs and resection of the stellate and upper four thoracic ganglia as well as vagotomy was done on four dogs. Changes in hemodynamics were consistent and precisely what were encountered in the control experiments. No more emboli were required to produce death than in the control series.

EXPERIMENTAL PROCEDURES AND RESULTS

In all experiments in which starch was the embolic agent a 1:2 suspension of cornstarch U.S.P. in saline solution was used. When barium was the embolic material insoluble barium sulfate U.S.P. in a 1:1 suspension was employed unless otherwise stated. The starch granules were round or polygonal and ranged from 10 to 90 microns in diameter averaging about 18 microns. The barium sulfate particles were the same shape but were generally larger averaging about 25 microns in diameter. Unless indicated to the contrary every animal was heparinized. Pentobarbital sodium and chloralose were the anesthetic agents.

Embolism With Starch in Rabbits and Dogs—Rabbits weighing 2 to 4 kilograms were used. They were heparinized and five minutes later the starch suspension was injected into an ear vein. This was followed by 1 cc of saline solution. The animal was then freed and observed.

Those that died showed the symptoms described by de Takats, Eck and Fenn² namely dyspnea, cyanosis and convulsions resulting in death in five minutes. The minimal lethal dose was found to be 1 cc of the suspension (Table I). Sublethal doses in the higher levels occasionally caused lethargy, dyspnea or possibly cyanosis and death. Most often there was not an effect from a sublethal dose.

The heart, lungs and brain of one animal from each group in Table I were examined microscopically for identification of the starch granules in these organs. In the lungs the starch granules were found scattered diffusely throughout the pulmonary arterial tree and lodged in great numbers in the capillaries. Occasionally a few were seen in arterioles. The arterioles were

TABLE I. RESULTS OF INJECTING 1 cc SUSPENSION OF CORNSTARCH U.S.P. INTO EAR VEIN OF HEPARINIZED RABBITS

RESULTS	0.5 cc	0.5 cc	1.0 cc	1.5 cc	2.0 cc
Died in five minutes or less		2	1	3	5
Did not die	3	3	4		

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usually greatly diluted. It was observed that the quantity of starch granules found in the lungs was increased in direct proportion to an increase in the amount of starch suspension administered to the rabbits. Occasionally the starch granules could be found in the heart, lodged in the capillaries but they were found in very small numbers only after long diligent search. Even more rarely, lesser numbers could be found in the capillaries of the brain after extensive examination. It is questionable whether the number of starch granules found occluding the capillaries of the heart and the brain of these rabbits was sufficient to have produced death.

Franzmetal and associates¹⁴ have shown that there are pulmonary arteriovenous anastomoses in anesthetized rabbits, cats, and dogs. They proved this by the injection of glass spheres suspended in saline solution into the right ventricle or pulmonary artery of the experimental animal and the demonstration that they could be recovered in the pulmonary veins and liver. The maximal size bead recovered varied from 160 to 290 microns in rabbits and 100 to 180 microns in dogs and measured 300 microns in one cat.

Nine dogs were used to determine the minimal lethal dose of the starch suspension when injected into a jugular vein or the right atrium. In each case the dog was anesthetized with pentobarbital sodium, the thorax was unopened, and the animal was heparinized. Simultaneous measurements of the carotid and right atrial pressures were recorded using a No. 10 French polyvinyl catheter, a water manometer for the latter and a mercury manometer for the former. When the starch suspension was injected into the right auricle the No. 10 French polyvinyl catheter recording its pressure was used. The starch was injected in graded doses proportionate to the kilogram weight of the dogs.

It was found that 0.5 c.c. of the suspension of starch per kilogram weight of the dog was the minimal lethal dose. This dose caused dyspnea, a sudden precipitous fall in systemic blood pressure to 20 or 30 mm. of mercury, and an average rise of 15 cm. of water in the right atrial pressure with death in two to five minutes in five dogs. Those animals given a sublethal dose of the suspension of starch had a drop in the carotid blood pressure of 30 to 50 mm. of mercury from which they recovered in less than one minute. In one animal there was another fall in the carotid pressure several minutes after the first, but the animal recovered. The right atrial pressure occasionally was altered showing a slight but never sustained rise in pressure. Dyspnea was seen in these animals only during this period. In those animals that died necropsy showed extreme dilatation of the right side of the heart with thrombi absent from the heart or lungs. Probably because of the scattering of the starch suspension throughout all lobes of the lung the starch could not be found grossly in the pulmonary arterial system. Four animals given sublethal doses were apparently unaffected and were killed one hour after the injection. These dogs were found to be normal with no evidence of dilatation of the right side of the heart, thrombi or starch except in one case in which moderate dilatation was seen. It was realized that the dogs killed at the end

of one hour might have died later from the injections of starch but that period of survival was arbitrarily chosen

To determine the influence of artificial insufflation of the lungs on the minimal lethal dose of the starch suspension two dogs were anesthetized with pentobarbital sodium and their thoraces were opened on the midline, their lungs being artificially inflated. The carotid and right atrial or right ventricular pressures were recorded with mercury manometers and the dogs were heparinized.

When a minimal lethal dose of the starch suspension was injected into the right atrium of one of the animals its blood pressure fell from 107 to 50 mm. of mercury in one minute and during the next five minutes the pressure rose to 80 mm. From this point the carotid pressure gradually fell, the right atrial pressure rose and the dog died thirty minutes after the injection. Necropsy showed the same findings as in the control series. The other animal when the minimal lethal dose of starch was injected had a sudden fall of carotid blood pressure from 110 to 30 mm. Then the pressure rose to 80 mm. In this animal the right ventricular pressure was recorded; it rose from 6 to 22 mm. of mercury when the injection was made and it held this level until several minutes before the animal died when it gradually fell to 2 mm. The carotid pressure gradually fell from 80 mm. to 0 in fifty-five minutes at which time the animal died. At necropsy the right side of the heart was moderately dilated but not distended with blood. Thrombi or starch could not be found in the heart or lungs.

Three dogs were used to determine the influence of bilateral cervicothoracic sympathectomy and cervical vagotomy in animals with open thorax on the minimal lethal dose of the starch suspension. They were anesthetized with pentobarbital sodium and the thorax was opened on the midline. Bilateral sympathectomy was done from the stellate ganglion to the fifth thoracic ganglion and then a bilateral cervical vagotomy was performed. The animals were heparinized after which a minimal lethal dose of the starch suspension was injected into the right atrium.

One animal died in three minutes after symptoms seen in the control series. The second animal had a fall in carotid pressure of 70 mm. of mercury but in one minute the pressure had returned to normal. Bigeminal cardiac rhythm then developed and lasted until the animal was accidentally killed at the end of thirty minutes. At necropsy it was found that the heart was moderately dilated on the right side and distended with blood. However thrombi or starch particles could not be found in the heart chambers or pulmonary arterial system. The third animal showed a response similar to that of the second dog. The carotid blood pressure fell 60 mm. of mercury and returned to normal in one minute. Trigeminal cardiac rhythm then developed and the dog died in fifteen minutes. Necropsy findings were the same as in the second dog.

The influence of bilateral cervicothoracic sympathectomy and bilateral vagotomy with closed

ginghion through the third intercostal space on each side and the thorax was closed. Then the procedure was continued as on the foregoing three dogs. These animals died in two minutes or less after the injection. The necropsy findings were the same as those in the control series.

Embolism With Iarium Sulfate in Dogs—Stimulated by the work of Smith and Harg,¹⁷ we performed the following experiments. Nine dogs weighing 7 to 23 kilograms were used (Table II). They were anesthetized and the thorax was opened on the midline. The carotid pressure was recorded in all experiments as a criterion of the animal's condition. A No. 9 French Courmand catheter was inserted into an external jugular vein and guided to a particular lobar artery according to the method of Kinney, Haynes and Dexter.¹ If the animal was to be heparinized it was done at this point. Then the 11 barium sulfate suspension was injected into the Courmand catheter and washed in with 2 cc. of saline solution the approximate capacity of the catheter. The injection was made quickly and forcefully in all dogs. Depending on the size of the dogs 2 to 8 cc. of the suspension was injected. In three dogs 0.5 cc. per kilogram of body weight was injected into the respective arteries. In some experiments the catheter was left in place and in others it was removed immediately after the injection to be reinserted if desired. Neither of these conditions seemed to influence the results. If the animal did not die within thirty minutes of the injection a pulmonary artery to another lobe was usually injected preferably on the side opposite to the previous injection and in two experiments a third injection was done.

If death did not result thirty minutes after a desired number of injections the animal was killed and the heart and lungs were removed en masse. Any roentgenograms desired were taken at this point before the heart and pulmonary vessels were opened thus avoiding disturbance of the anatomic and pathologic features. Then a careful examination of the heart was performed. Search was made particularly for thrombus formation, barium sulfate particles and dilatation of the right side of the heart. We dissected the pulmonary artery and its branches as far as the smallest vessels, running it temptingly to the left. To determine whether in four animals the injected barium sulfate entered the venous system as much as pentobarbital sodium. Heparin was used in only six of the nine animals.

Because Smith and Harg¹⁷ sometimes used a temporary constricting ligature about the artery proximal to the injection we employed their technique when administering the first injection to one animal.

Three of the nine animals died in two to seven minutes after the second injection of a lobar artery. In two of the three animals that died heparin was not used and their deaths both of which occurred in two minutes probably can be attributed to this fact for massive thrombi were found in the right auricles and ventricles of the hearts and in the pulmonary arteries. Death could conceivably have resulted from these thrombi. In one of these dogs the

TABLE II. EFFECT OF INJECTION OF A 1% SOLUTION OF INSOLUBLE BATH M SALT IN TO SPICATED FORMER LIGNONA ARGENTINOS OF ANASTOTIFIED DYES WITH OEN JOURNAL. THE IF WAS A 10 MINUTE LATE IN TWO INJECTIONS

[illegible]

roentgenogram revealed barium sulfate scattered throughout all lobes of the lungs, and in the other animal barium was seen in large amounts in the thrombi found in the heart and pulmonary artery. Evidently in these experiments there was a retrograde passage of the barium into the heart and death resulted. When the second lobar artery was injected in the third dog that died, its carotid pressure fell precipitously, the animal became tachypneic and died in seven minutes, with extreme dilatation of the right side of the heart. No thrombi or barium particles were present in the heart or pulmonary artery, and barium could be found only in the two lobar arteries injected. Whether there was a retrograde passage of the suspension with scattering into other lobes was not determined by roentgenogram. The possibility that this was the cause of death must be considered.



Fig. 1—Roentgenograms of (a) Dog 1 and (b) Dog 3 showing localization of barium sulfate in selected lobar pulmonary arteries.

In the remaining six dogs, one of which was not heparinized, there were no significant effects from injection of insoluble barium sulfate suspension into one, two, or three lobar arteries. Occasionally there would be a slight momentary decrease in the carotid blood pressure or an increased carotid excursion after an injection, but beyond this nothing significant occurred. In five of the six dogs, roentgenograms showed the barium sulfate in the injected arteries without scattering into other lobes (Fig. 1). After these dogs were killed, by stopping the artificial insufflation of the lungs, necropsy did not reveal pathologic findings. A difference in response that could be attributed to a change in the anesthetic agent from pentobarbital sodium to chloralose was not noted.

Thus using the Smith and Hara¹⁷ method in six dogs we were able to cause death in only one and in that case there remains the possibility that the dog died from multiple small emboli resulting from scattering of the barium sulfate throughout all lobes of the lungs. In three other dogs heparin was omitted and two of the animals probably died as a result of this omission.

In another series of experiments the foregoing technique was altered only as follows: six dogs anesthetized with pentobarbital sodium and heparinized were injected with a 5:4 suspension of barium sulfate (Table III). In five of them only the right lower lobar pulmonary artery was injected and the amount and rate were 3 cc in thirty seconds. The Courmand catheter used was of 2 cc capacity, so 5 cc was injected in fifty seconds to accomplish the foregoing result and to avoid the necessity to wash in the barium sulfate with saline solution, because this might cause a scattering of the embolic material into the other lobes of the lungs. After the injections the catheter was left in the injection position for the one hour control period at the end of which time the animal was killed by stopping the artificial insufflation of the lungs if death had not already occurred. In the case of the sixth animal two injections consisting of 2 cc of the suspension were administered one half hour apart at the rate of 1 cc per minute to the right middle lobar and left lower lobar pulmonary arteries respectively. During each injection a

TABLE III THE EFFECT OF INJECTION OF A 5:4 SUSPENSION OF INSOLUBLE BARIUM SULFATE INTO SELECTED LOBAR PULMONARY ARTERIES OF HEPARINIZED ANESTHETIZED DOGS WITH OPEN THORACES

DOG	WT (KG)	AMOUNT RATE AND SITE OF BARIUM SULFATE INJECTION	RESULT	POST MORTEM FINDINGS
10	6.8		30 mm of mercury fall in carotid pressure, 3 mm rise in right ventricular pressure, animal survived one hour then killed	
11	8.8		40 mm fall in carotid pressure and 4 mm rise in right ventricular pressure, animal survived one hour then killed	
12	16.6	3 cc barium sulfate into RLL artery in 30 seconds	4 mm fall in carotid pressure and 4 mm rise in right ventricular pressure, animal survived one hour then killed	
13	9.0		carotid pressure gradually fell to zero and right ventricular pressure gradually rose 10 mm in 50 min when dog died	Moderate right heart dilatation but no thrombi seen; no barium sulfate in left lung on microscopy
14	9.3			
15	7.0	2 cc RML artery in 2 min	None	No pathologic features noted
		2 cc LLL artery in 2 min	None	

In these injections a constricting ligature was placed temporarily around the artery proximal to the injection and released after each injection was completed.

constructing ligature was placed temporarily around the artery proximal to the injection and was released after each injection was completed

Of the first five dogs one died in fifty five minutes. They all showed within a few minutes a fall in the mean carotid arterial pressure of approximately 40 mm of mercury but in four dogs this level was maintained to the conclusion of the experiment. Simultaneously the mean right ventricular pressures rose, to 4 mm of mercury and were maintained. In the one animal that died the mean carotid arterial pressure continued to fall gradually to 0 in fifty five minutes and the mean right ventricular pressure had risen 10 mm of mercury above normal by the time death occurred. The sixth dog showed no response to the two injections. At necropsy pathologic features were not noted in any dog except the one that died. It exhibited moderate distention of the right side of the heart but no thrombi were seen. Barium sulfate could be seen grossly in the right lower lobar pulmonary artery. Roentgenograms were not taken in this series but microscopic examination of the left lung of the animal that died did not show that the embolic material had been scattered to the lung opposite to that injected.

COMMENT

In attempting to reproduce in animals the pulmonary embolic death seen in man from a disproportionately small blood clot experimental investigators have turned to the use of starch and barium sulfate as embolic agents. In explaining the mechanisms of death in both animals and man the investigators have divided into two schools of thought. The first postulates as the primary factor a nervous influence such as a vagal pulmonopulmonary or a pulmono coronary reflex. The second group states that the mechanical factor of obstruction of the pulmonary arterial system is the primary cause of death and that neurogenic factors play a negligible role if any.

The experiments of Megibow, Kitz and Steinutz demonstrate the result if a minimal obstruction of the pulmonary venous return is created. They injected smaller amounts of starch granules into the pulmonary arterioles and capillaries than were used in our experiments. In one half of their animals they injected the starch suspension in divided doses. They noted that the elevation in the systemic venous pressure associated with a normal systemic arterial pressure persisted in some animals until death. This demonstrated the result of an obstruction of the pulmonary arterial system sufficient to place an increased load on the right side of the heart without reducing the cardiac output causing gradual failure of the right ventricle. In other animals in spite of an elevated pulmonary arterial pressure both the systemic arterial and the venous pressures tended to decrease reaching shock level in some instances just before the animals died. This showed the result of an obstruction of the pulmonary arterial tree sufficient to reduce the cardiac output in addition to placing an increased load on the right side of the heart resulting in a reduction in the volume of blood circulating in the peripheral vascular tree, leading to a peripheral vascular collapse.

In our experiments a more complete and dramatic obstruction was achieved, resulting in an immediate, almost complete diminution of the cardiac output relative coronary insufficiency myocardial ischemia and death. In the control group the animals given the "minimal lethal dose" demonstrated simultaneously a rise in right atrial pressure of 15 cm of water and a precipitous drop in carotid arterial pressure to 20 or 30 mm of mercury with death in two to five minutes. When the sympathetic chain from the stellate ganglion to the fifth thoracic ganglion was sectioned bilaterally and subsequently a bilateral cervical vagotomy was performed prior to the injection of a 'minimal lethal dose' of the starch suspension little alteration in the results from those found in the control group was noted. Thus we were unable to note the influence of any neurogenic factors in the death of the animals given this dosage of a starch suspension.

In another study related to the neurogenic hypothesis of death from pulmonary embolization by particulate matter an attempt was made to reproduce in twelve dogs the work of Smith and Hara¹¹ using a barium sulfate suspension. In only two dogs was death produced in spite of the fact that two or three lobar arteries were injected in some animals. An intense vasospasm the response to stimulation of neuroreceptors in the walls of pulmonary vascular system by the embolic material is considered by some authors including Smith and Hara to be the cause of death in embolism of the pulmonary arterioles and capillaries. This is further suggested by the work of Haynes Kinney Hellem and Dexter¹². It is believed by some that these stimuli elicit a massive reflex vasospasm of the pulmonary vascular bed and that death is caused by this reflex vasospasm not by the simple mechanical obstruction of the arterioles and capillaries. In our first series of injections of a selected lobar artery care was taken in the injection of the embolic material to exert as much pressure as was possible within the artery. Significant responses were not elicited by these forceful injections except in one animal and in that animal it is probable that the force of the injection succeeded only in causing a retrograde scattering of the embolic material throughout the lungs.

Furthermore as was previously mentioned Haynes Kinney Hellem and Dexter¹² obstructed and distended a lobar pulmonary artery by dilating a balloon on the end of a venous catheter in that artery with a pressure higher than that in the main pulmonary artery. They were unable to note any constant change in the respiratory rate pressure in the femoral and pulmonary arteries and the heart rate of anesthetized and unanesthetized dogs. It is also important to note accepting the minimal lethal dose of a 1:2 starch suspension established and presuming cornstarch and barium sulfate to be pulmonary embolic agents equal in all respects that twice the dose of barium sulfate which is lethal when given into a peripheral vein was injected directly into each of two lobar pulmonary arteries at intervals of thirty minutes in three dogs anesthetized with chloralose. Only one of these three dogs died and that was probably because heparin was omitted in the experiment. In the second series of injections of a selected lobar artery death was produced in

one animal of six in which a slightly different procedure was used. That the mean systemic blood pressure was lowered in all animals and that this fall was the probable cause of death in one is interesting and suggestive, but inconclusive evidence of reflex vasospasm in the pulmonary arterial system.

SUMMARY AND CONCLUSIONS

In these experiments it has been shown that

1 A standard dose of 1:1:2 suspension of cornstarch injected into a peripheral vein in heparinized rabbits will cause death in every instance, a fact that supports the work of de Takats, Beck and Penn,³ and the conclusion that death is the result of lodgment of the starch particles in the arterioles and capillaries of the lungs and not in the heart or brain.

2 A similar standardization was established in anesthetized, heparinized dogs.

3 The result of such an injection was not altered by bilateral cervical vagotomy following bilateral sympathetic ganglionectomy from the stellate ganglion to the fifth thoracic ganglion in a series of dogs.

4 Death was produced in only one of six anesthetized heparinized dogs from the forceful injection of 1:1:1 suspension of insoluble barium sulfate into one, two, or three selected lobar pulmonary arteries.

5 In only one of six anesthetized heparinized dogs was death caused by the slow injection of a 5:4 suspension of insoluble barium sulfate into a selected lobar pulmonary artery.

REFERENCES

- 1 Churchill F. D. Mechanism of Death in Pulmonary Embolism. With Comments on the Experimental Aspect. *Ann Surg* 66: 193-194, 1917.
- 2 Katz I. N. Experimental Pulmonary Embolism. *Am J Path* 19: 1-10, 1913.
- 3 De Takats, Beck and Penn. *Am J Path* 19: 1-10, 1913.
- 4 Cobb W. J. The Pulmonary Artery and Its Lobar Branches. *Ann Surg* 66: 193-194, 1917.
- 5 Hall E. D. Changes in the Circulation of the Pulmonary Artery. *J Clin Investigation* 11: 1-10, 1932.
- 6 Haggart C. E. and Walker A. M. The Physiology of Pulmonary Embolism as Disclosed by Quantitative Occlusion of the Pulmonary Artery. *Arch Surg* 6: 761-762, 1903.
- 7 Hall G. F. and Pittenger G. H. An Experimental Study of Pulmonary Embolism. *Canad M A J* 28: 367-368, 1933.
- 8 Holden W. D., Shaw B. W., Cameron D. B., Shea F. J. and Davis J. H. Experimental Pulmonary Embolism. *Surg Gynec & Obst* 88: 330, 1949.
- 9 Malinow M. R., Katz I. N. and Kondo H. Is There a Vagal Pulmonary Coronary Reflex in Pulmonary Embolism? *Am Heart J* 31: 710, 1946.
- 10 Mann F. C. Pulmonary Embolism. An Experimental Study. *J Exper Med* 26: 327-333, 1917.
- 11 Megibow R. S., Katz I. N. and Feinstein M. Kinetics of Respiration in Experimental Pulmonary Embolism. *Arch Int Med* 71: 336-346, 1943.
- 12 Mendelowitz, M. Experimental Pulmonary Embolism. *J Thoracic Surg* 8: 201-212, 1933.
- 13 Binger, C. A. I., Brown G. R. and Branch Arnold. Experimental Studies on Rapid Breathing. II. Tachypnea Dependent Upon Anoxemia Resulting From Multiple Emboli in the Larger Branches of the Pulmonary Artery. *J Clin Investigation* 1: 15-20, 1934.

14 Haynes F W, Kasper T D, H - W - - - -
15 Kinn
16 Prin
17 Smith J R, and Hara Masao¹⁹⁴⁵ Experimental Embolism of Selected Portions of Pulmonary Arterial Bed Federation Proc 7 117, 1948
18 Binet Léon and Burstein M Nouvelles recherches sur l'embolie pulmonaire expérimentale Proc méd 54 633 f3, 1946
19 Binger, C A L, Brow G I and Branch Arnold Experimental Studies on Rapid Breathing I Tachypnea Independent of Anoxemia Resulting From Multiple Emboli in the Pulmonary Arterioles and Capillaries, J Clin Investigation 1 127 153 1944
20 Dunn J ^a The Effects of Multiple Embolism of Pulmonary Arterioles Quart J Med 13 129 147 1920
21 Flasher, J, Essex H E and Barne A R An Experimental Study of Acute Pulmonary Arterial Obstruction With Special Reference to the Precordial Electrocardiogram Am Heart J 36 882 892 1948
22 Megibow I S, Katz L N and Steinitz F S Dynamic Changes in Experimental Pulmon - Embol - - - -
23 Villaret N Recherches sur la prevention e
24 Jeser J Pulmonary Artery During Its Ex

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This is a critical review of the whole problem of the physiology and pharmacology of fetal respiration. A good review establishes for the fact that interference with fetal respiratory mechanisms is responsible for a large part of neonatal mortality and morbidity. The author explains at length the techniques which he has used for the objective evaluation of the effect of drugs on the respiratory reflexes. This has been previously published but is brought together in this monograph and is related to the work of others. There is a somewhat brief discussion of the practical details of the various methods of analgesia and anesthesia in obstetrics.

This is an excellent book and contains information essential to anyone working in obstetrics. It is not a practical guide to obstetric analgesia and anesthesia. However the theoretical background presented here is probably more useful. It is a welcome authoritative and condensed source of basic data.

Books Received

The receipt of books is acknowledged in this section and this treatment must be regarded as sufficient acknowledgment of the courtesy of the sender. Selections will be made for more extensive review dictated by the interests of our readers and as space permits.

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delphia, 1949, W B Saunders Company

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Springfield 1949 Charles

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University of Illinois Cloth. Price \$6 Ed 1 Pp 50 with 140 illustrations Chicago, 1949 Williams & Wilkins Company

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No 5

Original Communications

THE HUMAN HEART RATE

SOME OBSERVATIONS AND DEDUCTIONS BASED UPON THE EFFECT OF REMOVING PORTIONS OF THE SYMPATHETIC NERVOUS SYSTEM IN MAN

R H SMITHWICK MD E M CHAPMAN MD D KINSFY, MD, AND
G P WHITFLAW MD BOSTON, MASS

CHAPMAN Kinsey Chapman and Smithwick¹ in 1948, presented their preliminary observations on the effect of removing the motor pathways through which the cardioaccelerator fibers are transmitted to the human heart. They concluded that removal of the right and left second third, fourth and fifth thoracic sympathetic ganglia produced a marked reduction in basal pulse rate as well as a diminished acceleration following exercise and hence motor pathways (cardioaccelerator fibers) to the human heart appeared to be derived from both the right and left second third fourth and fifth thoracic sympathetic ganglia. It was suggested that this procedure might be of therapeutic value in the control of tachycardia and possibly other disturbances of cardiac rhythm in selected patients. The data to be presented in this paper more thoroughly substantiate these original conclusions.

Von Bezold² in 1863, Hunt³ in 1899 and Krogh and Lindhard⁴ in 1913 made major contributions to our knowledge of the vagus effect on the heart rate as well as the manner in which this effect occurs. In addition Hunt³ studied extensively the action of cardioaccelerator nerves to the heart in animal experimentation and demonstrated tonic activity of the accelerators. However it must be remembered that work done on the cardiac accelerator mechanism prior to the paper of Cannon and associates in 1926 did not take into consideration the existence of cardio accelerator fibers below the first dorsal ganglion.

Langley⁵ in 1892 demonstrated that accelerator impulses to the heart leave the cord by the upper five pairs of anterior roots and their white rami. He was in error however regarding the transmission of these impulses through the cervical cardiac nerves. Cannon and associates⁶ in 1926 demonstrated in animals that accessory cardiac accelerator fibers are carried to the heart in branches of the thoracic sympathetic nerves that lie below the

stellate ganglion. This important observation was soon verified by Braeucker⁷ and Ionescu Fuachescu and Teitel.⁸ Kuntz and Morehouse⁹ demonstrated by anatomic dissections on post mortem human hearts that cardioaccelerator nerves direct to the human heart come from the second, third, fourth and fifth thoracic ganglia of the sympathetic nervous system. Saccomanno Utterback and Klemme¹⁰ confirmed these findings in dogs by using a special preparation and recording the effect of stimulating various upper thoracic nerves.

White and Bland 1945¹¹ stated: "Concerning the interruption of motor impulses which drive the heart to exceed its limited capacity for work, the experiments of White Garvey and Atkins showed that to accomplish this it is necessary to perform extensive upper thoracic ganglionectomy on both sides. It is also necessary to eliminate the secretion of the adrenal medullas because Cannon, Lewis and Britton have found that the denervated heart is accelerated by minute quantities of adrenaline. If it were practical to do this the heart would be seriously crippled thereby. Our clinical observations have shown that all the sympathetic cardiac nerves can be interrupted and still permit the heart an adequate accelerator response through reduction in vagal tone and the chemical mediation of adrenaline and sympathin."

There is apparently some confusion in the literature regarding the terms 'sympathectomized' and 'denervated' as applied to the heart. Indeed the denervated heart may be accelerated by minute quantities of adrenaline but in any case there is no confirmation of this in the paper of Cannon and co-workers 1926. Even though the denervated heart were accelerated by minute amounts of circulating adrenaline and sympathin it would not necessarily follow that the sympathectomized heart would be accelerated likewise by minute amounts of adrenaline and sympathin as the vagal tone might well counter balance any effect of the chemical mediators.

Chapman Kinsey Chapman and Smithwick¹ inferred that White and Smithwick¹² on page 281 of their book said that by total sympathectomy the heart would be undoubtedly greatly crippled. What White and Smithwick¹² actually meant was that by total cardiac denervation plus adrenalectomy or adrenal denervation the heart would undoubtedly be greatly crippled. There is no doubt that this would be the case. Such a procedure of course would be out of the question to consider in man.

Chapman Kinsey Chapman and Smithwick¹ stated that: "The effect of sympathectomy on heart rate was no greater in those patients who had splanchnic denervation supposedly including the adrenals than those who had cardiac (2nd to 5th dorsal ganglion) denervation only. This matter will be more fully discussed in a separate communication in the near future and the summary of our clinical observations given at that time."

In 1936 Bronha Cannon and Dill¹³ showed that totally sympathectomized dogs run jump play and look like normal dogs and yet after exercise their pulse rates were 30 to 40 per cent below those of normal dogs. In 1938 Smithwick had done a total sympathectomy on a hypertensive man

without ill effects and noted that bradycardia was present. Adson and Brown¹⁴ reported that they had not observed any diminution of pulse acceleration after effort when the first two thoracic ganglia bilaterally had been severed in one case.

An objection to cardiac sympathetic denervation might be raised in reference to possible adverse effects on coronary circulation particularly in cases of angina pectoris. The controversial question of the innervation of the coronary vessels has not as yet been answered. Anrep and Segall¹⁵ by use of a complicated preparation in a dog reached the conclusion that the sympathetic nerves caused coronary vasodilatation whereas stimulation of the vagus nerves caused coronary vasoconstriction. Kountz, Pearson and Koenig¹⁶ in working with revived human hearts were not able to support the conclusions of Anrep and Segall. Katz and Joehim¹⁷ in studying the innervation of the coronary vessels of the dog found that stimulation of the sympathetic nerves to the coronary vessels predominantly produced vasoconstriction. It will be seen therefore that different workers in this field have reached diametrically opposed conclusions. From a practical standpoint, patients who have had sympathetic cardiac denervation have not had any adverse effect on the coronary circulation in so far as has been determined from a clinical evaluation of our cases.

The idea leading to the observations of Chipman, Kinsey, Chapman and Smithwick¹ came from patients who had thoracic sympathetic nerves severed for other indications and later noted that their pulse rate was slower and that exercise did not cause as marked an increase in heart rate as before sympathectomy. Attention was thereby directed to the possible control by surgical methods of disabling exertional or emotional tachycardia and other disturbances of cardiac rhythm. Nineteen patients who had thoracic sympathetic ganglia removed from one or both sides were discussed in their paper.

Clinical Material—This present report deals with the effect on the pulse rate of thirty seven patients who have had different portions of the thoracic sympathetic chain removed from one or both sides for various purposes such as disabling emotional or exertional tachycardia, angina pectoris, coronary artery heart disease with or without associated hypertension, vasomotor disorders of the upper extremities and hyperhidrosis with or without vasomotor involvement. These studies were done on the pulse rate response to exercise of patients before and then at intervals after removal of the thoracic sympathetic ganglia first on one side and later after the second stage on the opposite side. The pulse rate recordings were obtained from a slight modification of the two step exercise test as described by Master, Nuzie, Brown and Larker¹⁸. This is described later in more detail. The levels of resection were later verified by x ray identification of clips left at the operative site by the presence or absence of Horner's sign, by skin resistance studies and by surface temperature determinations.

From March 1946 until March 1948 117 patients had thoracic sympathectomy performed by us for one of the aforementioned reasons. Most of the procedures have been bilateral at separate stages making a total of 199 opera-

quate stimulus for cardiac acceleration and did not exceed the exertional capacity of patients who had coronary heart disease with angina pectoris or hypertension or both. In a few patients, a more strenuous test devised by one of us (E. M. C.) was used. In this after a preliminary rest period, the patient steps up and down one 16 inch step thirty times in one minute. Control observations for each test were made in two series of young healthy, supposedly normal individuals. These are illustrated by Figs 1 and 2. The top of the crosshatched area indicates the highest rates of the various individuals of the series and the bottom of the crosshatched area indicates the lowest rate of the individuals used in this series. The heavy solid line is the

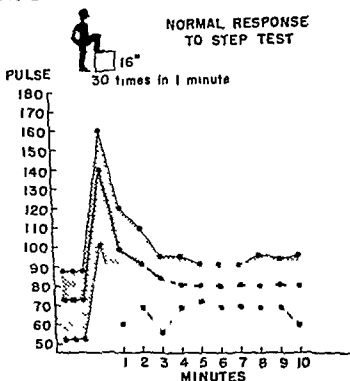


Fig 2.—Normal response of a series of fifteen young healthy supposedly normal individuals to the modified "one-step" exercise test.

average of all those tested. These tests were performed before and after unilateral and after bilateral procedures in the great majority of patients, and before and after both operations in a few. The data furnish information concerning the neurogenic control of the human heart rate and are of a variety previously unavailable except for a preliminary report by several of us concerning this matter. We were particularly interested in obtaining further information bearing upon the origin of the cardioaccelerator fibers from the cord, the relative effect of unilateral and bilateral cardiac denervation, the role of the parasympathetic and the sympathetic divisions of the autonomic nervous system in the control of the resting heart rate and of the accelerator

response to exercise and possible clinical application for cardiac denervation (sympathetic motor)

Information bearing upon these matters was obtained by grouping patients according to the operative procedure performed and studying the re-

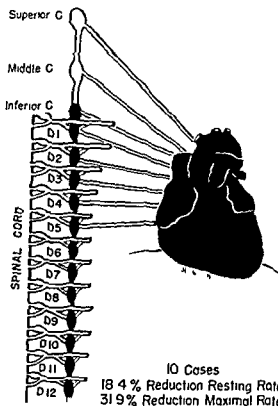


Diagram 1—Effect of removing inferior cervical or D through D or D in twelve in ten cases

sults of the step test before and after each operation. Data having to do with the upper limit of the sympathetic outflow from the cord are summarized in Table I. The effect of bilateral operations in twenty one cases upon the control heart rate and the maximal the two minute five minute and ten minute

TABLE I

GROUP	NO. CASES	OPERATION	EFFECT	RESTING	MAXIMAL	2 MIN	5 MIN	10 MIN
1	10	Inf C or T ₁ to T ₁ or T ₂ inclusive	% Reduction	18.4	31.9	16.3	27.8	21.5
2	10	T ₂ to T ₁ or T ₁₂ inclusive	% Reduction	21.3	31.7	17.7	26.5	24.6
3	1	T ₁ to T ₁ or T ₁₂ inclusive	% Change	+2.3	+12.0	+3.4	-4	0.0

The data in this table have to do with the upper level of outflow of the cardioacceleratory fibers from the thoracic cord. They indicate that the outflow from the first thoracic segment in man is not important but that the outflow from the second segment is important and probably is the upper level. All operations were performed bilaterally.

rates after exercise is expressed in terms of percentage reduction in rate after the different procedures. The first group consists of ten cases in which all possible connections between the cord and the heart were removed. This is shown schematically in Diagram 1. In this and subsequent diagrams the blacked out ganglia represent those removed. In these cases the upper limit of the resection included the inferior cervical or the first thoracic ganglion or both and the lower limit extended as low as the eleventh or twelfth thoracic ganglion inclusive (see Fig 3). The second group consists of ten

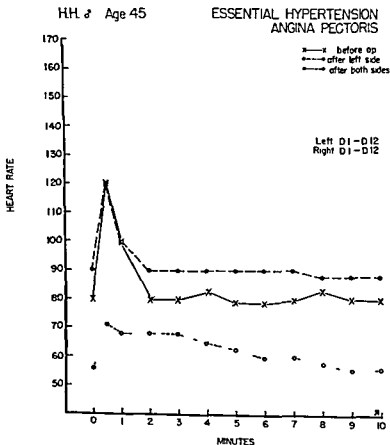


Fig 3—The exercise test in a case of hypertension combined with angina pectoris

cases in which the upper limit included the second thoracic ganglion and the lower limit was the same as in the first group. (See Diagram 2 Fig 4 and Table I Group 2). The only difference between the operations in the two groups was that any cardioaccelerator fibers which emerge from the first thoracic segment were not interrupted in the second group. The effect of operation in the two groups as judged by the percentage reduction in heart rate was almost identical. This indicates quite conclusively that few if any cardioaccelerator fibers leave the cord by way of the first thoracic segment.

ESSENTIAL HYPERTENSION ANGINA PECTORIS EXERTIONAL TACHYCARDIA

FA ♀ Age 35

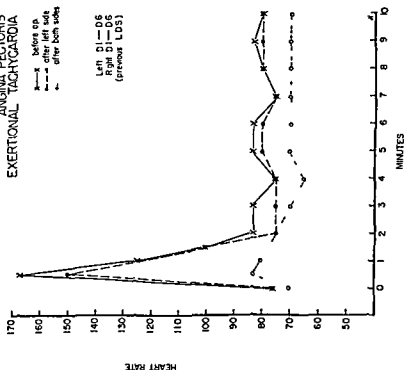


Fig 5

This case had previous bilateral lumbo

ESSENTIAL HYPERTENSION EXERTIONAL TACHYCARDIA

RH ♀ Age 44

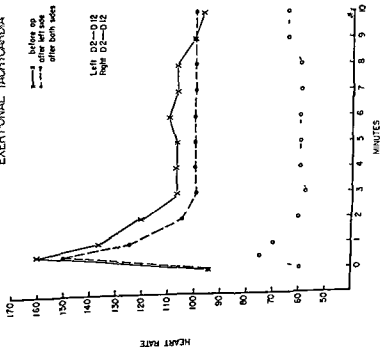


Fig 4

Fig 4—The exerci e test in the case of hypertension and exertional tachycardia.

Fig 5—The exerci e test in the case of hypertension angina pectoris and exertional tachycardia This case had previous bilateral lumbo

dorsal splanchnicectomy

In one case the sympathetic trunks were removed bilaterally from the third to the eleventh or twelfth thoracic ganglia, inclusive thus leaving the outflow from the second thoracic segment intact. There was essentially no resultant effect upon heart rate. (See Diagram 3 Fig 7, and Table I, Group 3.) This indicates that the outflow from the second thoracic segments is of great importance and together with the preceding observations tends to place the upper limit of outflow of cardioaccelerator fibers from the cord at the second thoracic segment. These findings are in keeping with the observations of Kuntz and Morehouse⁸ in post mortem human heart dissections and Saccomanno, Utterback and Klemme¹⁰ derived from experiments on dogs.

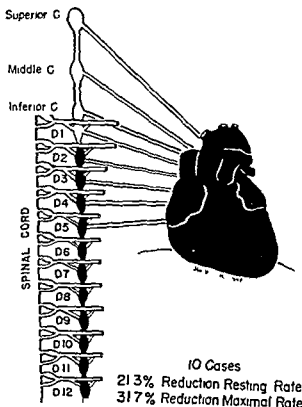


Diagram 2.—Effect of removing D₃ through D₁₂ or D₃ inclusive in ten cases

Data bearing upon the lower limit of the cardioaccelerator outflow are summarized in Table II. Since it was believed that the first thoracic segment had been excluded from consideration all operations in which the upper limit of the resection included the second or first thoracic ganglion or the inferior cervical ganglion and in which the lower limit included the sixth to the twelfth thoracic ganglia bilaterally were grouped together. The lower limit was set at the sixth ganglion since direct connections with the human heart have not been described as low as this level. This group (Table II,

Group A) of cases included Groups 1 and 2 in Table I and in addition six other cases in which the lower limit included the sixth to the ninth ganglia, the upper limits being the same making a total of twenty six cases (see Diagram

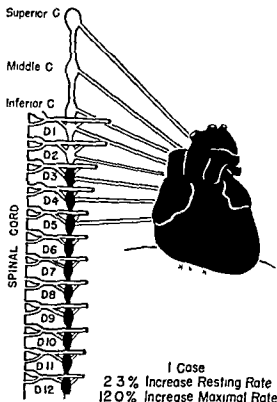


Diagram J—Effect of removing the thoracic chain below D₆ bilaterally (see Fig 7)

4) The effect of operation in these cases is compared with that of lesser resections performed in two smaller groups. The first of these (Table II Group B) is composed of six cases in which the operative procedures were

TABLE II

GROUP	NO. CASES	OPERATION	EFFECT	RESTING	MAXIMAL	1 MIN	5 MIN	10 MIN
A	26	Inf C to T through T to T inclusive	P reduction	147	332	208	206	113
B	6	T ₁ T ₂ or T ₁ T ₂ inclusive	C reduction	43	218	59	44	04
C	4	T ₂ T ₃ T ₄ T ₅ inclusive	C reduction	289	35	316	300	27

the equivalent of removing the second and third or the second, third, and fourth thoracic ganglia bilaterally (see Diagram 5). The last group (Table II, Group C) contains four cases in which the sympathetic trunks were removed bilaterally from the second to the fifth thoracic ganglion inclusive (see Diagram 6 and Fig. 6). It will be noted that the effect of operation upon heart rate is marked and probably maximal in Groups A and C, being distinctly less in Group B. This indicates that the outflow from the fourth and fifth thoracic segments is of importance. That the outflow from the third segment is also of consequence can be safely presumed. These findings are consistent with the belief that the lower limit of outflow of cardioaccelerator fibers is the fifth thoracic segment.

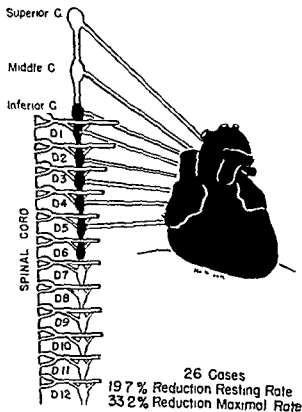


Diagram 4.—Effect of removing inferior cervical to D₂ through D₄ to D₁₂ inclusive in twenty-six cases.

EFFECT OF UNILATERAL SYMPATHETIC CARDIAC DENERVATION

It has been apparent from the beginning of this study that complete unilateral sympathetic denervation has only a slight effect upon heart rate. Occasional cases are exceptions to this rule, but if the effect of operation is averaged for all cases having a unilateral denervation it will be found that there is very little change from the preoperative data (Table III). If however, the

EXERCUTIONAL TACHYCARDIA

A.M.C. ♀ Age 4)

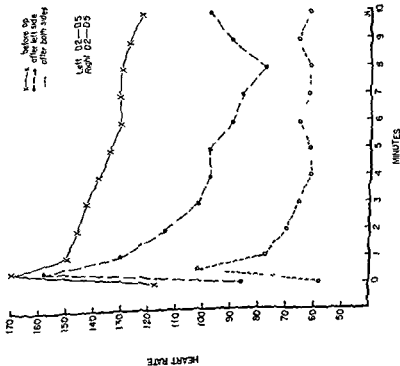


Fig 6

Diagram 6

Fig 6—The exercise test in a case of exertional tachycardia without angina pectoris or hypertension.
Fig 7—The exercise test in the previously mentioned case of hypertonia in which the second dorsal ganglia were left intact bilaterally (see Diagram 7).

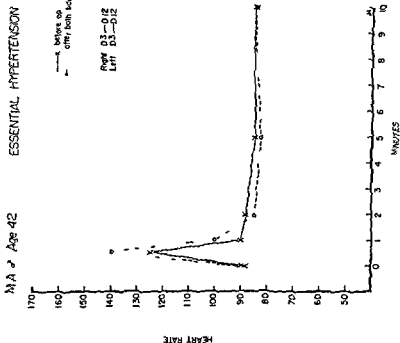


Fig 7

Fig 7—The exercise test in a case of essential hypertension without angina pectoris or hypertension.
Fig 8—The exercise test in the previously mentioned case of hypertonia in which the second dorsal ganglia were left intact bilaterally (see Diagram 8).

effects of left and right sided operations are compared, it is apparent that, in general right sided denervations have only a slightly greater effect (Table III). The difference is definite and indicates that the cardioaccelerator outflow from the right side is slightly greater than from the left. The effect of

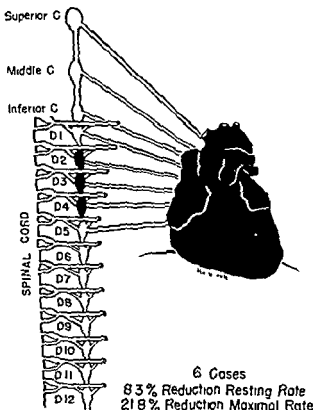


Diagram 5—Effect of removing D₁ and D₂ or D₃ D₄ and D₅ inclusive in six cases

TABLE III

OPERATION	NO. CASES	AVERAGE OF PREOPERATIVE RATES					% CHANGE IN RATE POST OPERATIVELY				
		BEST ING	MAX IMAL	2 MIN	5 MIN	10 MIN	BEST ING	MAX IMAL	2 MIN	5 MIN	10 MIN
Unilateral denervation	29	82	129	0	59	90	-13	-58	-21	-38	-18
Denervation of left side	19	50	129	00	57	84	-93	-15	+19	-06	+03
Denervation of right side	10	5	127	97	93	90	-14	-112	-93	-94	-57

In this table the effect of unilateral cardiac denervation was noted with regard to which side was a minimal reduction. The effect upon heart rate was slightly slower or faster. In light but definite reduction these data indicate that the

a right sided denervation is however, far less than that of a bilateral procedure. It would seem as though a unilateral procedure would probably not be of any practical therapeutic value in the control of rapid heart rates.

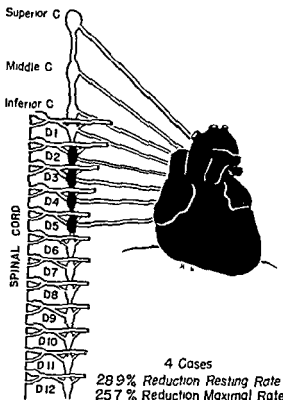


Diagram 6—Effect of resecting D₁, D₂, D₃, and D₄ inclusive in four cases.

THE ROLE OF THE VAGUS AND THE SYMPATHETIC NERVES IN THE CONTROL OF THE HEART RATE

There are many factors which may affect the heart rate. Among these are variations associated with respiration, variations in blood carbon dioxide and oxygen content, variations in body temperature, intracranial pressure, and the quantity of adrenaline, sympathin, acetylcholine, thyroxine, and vasopressin which may be in circulation. If we exclude these from this discussion on the presumption that there was no very great alteration of any of these factors in these patients, the effect of operation may be interpreted in terms of vagal denervation. Changes in blood pressure are of importance, but that would tend to decrease the heart rate.

With these various factors in mind, the thirty patients having what we believe to be totally sympathetomized hearts were divided into two groups.

according to the preoperative resting heart rate. Those with resting rates below 80 were placed in the first and those with rates of 80 or more in the second. There were fourteen cases in the former (Table IV, Group 1) and sixteen cases in the latter (Table IV, Group 2). It is of interest that the percentage reduction in the pulse rate following operation is several times as great in the faster rate group. This suggests that the faster the resting heart rate the greater is the imbalance between the vagus and the sympathetic. On the other hand, the final pulse rates in the faster rate group are higher than in the slow rate group, suggesting that the increased heart rate might not have been entirely due to increased sympathetic tone but may have been partly due to a decrease in vagal tone. Otherwise the final rates should theoretically have been the same in the two groups. It is also of interest that following sympathectomy there was a decrease in heart rate in the slow rate group. In fact of the thirty cases under discussion only 3 failed to show a definite slowing of the resting rate after operation. This suggests that the vagus and the sympathetic are both tonically active in man.

TABLE IV

GROUP	PREOPERATIVE RESTING PULSE RANGE	NO. CASES	AVERAGE PREOPERATIVE RESTING RATES	AVERAGE POSTOPERATIVE RESTING RATES	AVERAGE REDUCTION
1	55-79	14	64	60	7%
2	80-128	16	91	69	23%

The percentage reduction in resting pulse rate after complete cardiac sympathectomy is almost three times as great in the faster pulse rate group (Group 2). The fact that the final rates are higher in the faster rate group is of interest. This imbalance between the vagus and the sympathetic is probably the cause of the imbalance between the two groups but the fact that the faster rate group has a more active sympathetic system is also a factor.

With regard to the effect of exercise upon the heart rate it is of interest that the percentage increase in the maximal rate before operation was nearly twice as great in the slow as in the rapid heart rate groups although the maximal rates were higher in the second group (Table V, Groups 1 and 2). After operation the percentage increase in maximal rate following exercise was exactly the same in the two groups. Such a response is probably mediated by a reflex mechanism in which afferent impulses from the great veins entering the right side of the heart reach the cardiac center by way of the vagus and inhibit vagus tone thus causing an increase in heart rate. The decreased percentage increase in heart rate to the stimulus following operation indicates that a significant portion of the accelerative mechanism in the normally innervated state is due to stimulation of the sympathetic outflow superimposed upon vagus inhibition.

TABLE V

GROUP	PREOPERATIVE RESTING PULSE RANGE	NO. CASES	AVERAGE PREOPERATIVE MAXIMAL RATE	INCREASE ABOVE RESTING RATE	AVERAGE POSTOPERATIVE MAXIMAL RATE	INCREASE ABOVE RESTING RATE
1	55-79	14	115	50%	81	30%
2	80-128	16	134	46%	93	30%

a right sided denervation is however far less than that of a bilateral procedure. It would seem as though a unilateral procedure would probably not be of any practical therapeutic value in the control of rapid heart rates.

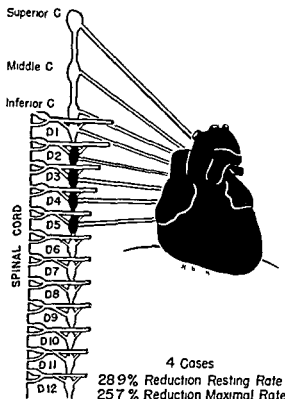


Diagram 6—Effect of removing T₁, D₁, D₂ and D₃ inclusive in four cases

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With these various factors in mind the thirty patients having what we believe to be totally sympathetomized hearts were divided into two groups

No untoward effects have followed resection of the cardioaccelerator fibers in man in our experience.

- 1 Chapman E M Kiley D Chapman W P and Smithwick R H Sympathetic Innervation of the Heart in Man Preliminary Observations of the Effect of Thoracic Sympathectomy on Heart Rate J A M A 137 579-84 1948
- 2 Von Bezold A Untersuchungen über die Innervation des Herzens Leipzig 1863, Wilhelm Engelmann
- 3 Hunt Reid Direct and Reflex Acceleration of the Mammalian Heart With Some Notes on Vagus Nerves Am J Physiol 1910
- 4 " " " " d Circulation During Asphyxia Arch Int Med 1910
- 5 " " " " Cervical and Upper Thoracic Sympathectomy White and Gray Ramus Communis Brachii J Neurosurg 1952
- 6 I R and Linton R R Studies on the Conditions of Activity in Endocrine Glands VII A Lasting Preparation of the Denervated Heart for Detecting Internal Secretion With Evidence for Accessory Accelerator Fibers From the Thyroid Gland J Clin Invest 1952
- 7 Brauer C Die Beziehungen zwischen den vegetativen Nervenzentren und dem Kreislaufsystem und seine klinische Bedeutung Berlin 1907
- 8 Ionescu S Ueber eine neue Gruppe von Sympathischen aus dem Brüdgrenzstrang unterhalb des Ganglion stellatum ent springenden Herzerven Klin. Wchnschr 7 691 1928
- 9 Kantz A and Morehead F Relation to Cervicodorsal Sympathy J Surg 1928
- 10 Saccomanno G Utte The Surgical Treatment of Cervicodorsal Sympathy Ann Surg 1928
- 11 White James G and Johnston Methods of Treating Cervicodorsal Sympathy JAMA 1938

POSSIBLE CLINICAL APPLICATIONS FOR RESECTION OF CARDIOACCELERATOR FIBERS

The majority of the operations upon which these observations are based were performed for the relief of angina pectoris with (see Fig 3) or without hypertension. In others, the operations were performed for the relief of vaso spasm or hyperhidrosis of the upper extremity. However, in ten cases, hypertension associated with an unusual degree of tachycardia was the reason for including the heart in the denervated area (see Fig 4). In these cases, the sympathetic trunks were removed bilaterally from the second to the eleventh or twelfth thoracic ganglia inclusive, in addition to the greater and lesser splanchnic nerves. We have found that in cases of this sort splanchnicectomy alone may be followed by an increase in tachycardia. In a few cases this has been so distressing that subsequent cardiac denervation has been necessary (see Fig 5). The early results of near total thoracic sympathectomy in this particular group of hypertensive patients appears to have been helpful.

In four cases disabling tachycardia for which no cause other than neurogenic imbalance could be found, was the reason for cardiac denervation (see Fig 6). In two of these, the resting rates were rapid and rose markedly upon slight exertion. These patients may fall into the category of neurocirculatory asthenia. Both were greatly improved following operation. In the other two cases, the basal rates were higher than normal but the accelerator response to exercise was not remarkable. Both however suffered from severe disabling tachycardia upon emotional stimulation such as meeting strangers or taking examinations. Psychotherapy had been of no avail. Both are greatly improved following operation.

It has been thought that sympathetic motor denervation of the heart might be of help in the management of refractory forms of paroxysmal auricular tachycardia.¹⁵ We have performed cardiac sympathectomy in two such cases. In one case the first to the sixth thoracic ganglia were removed on both sides. Paroxysmal auricular tachycardia returned some months later although we have no electrocardiographic representation of the attacks in this case. In the second case in which severe disabling paroxysmal auricular tachycardia occurred in a young woman denervation was carried out on both sides from the second to fifth thoracic ganglia inclusive. Attacks recurred following this procedure. The stellate ganglia were removed on both sides at a later operation. The paroxysmal auricular tachycardia again recurred after this procedure. All of these attacks are recorded electrocardiographically. In both of the cases mentioned the recurrent attacks were of marked shorter duration and occurred with much less frequency than before operation and in one case at the end of two years the attacks have virtually ceased. This would indicate that cardiac sympathectomy can be effective in certain cases of this type.

SUMMARY

Evidence is presented which suggests that the cardioaccelerator fibers in
- the cord inclusive

STAB WOUND OF THE HEART FOLLOWED BY TEMPORARY CESSATION OF THE HEARTBEAT WITH RESUSCITATION BY CARDIAC MASSAGE

A CLINICOPATHOLOGIC STUDY OF ONE CASE OF THIRTY DAYS' SURVIVAL

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RECORDED cases of cessation of the heartbeat and resuscitation by manual massage are numerous. Barber and Madden¹ in reviewing the literature up to 1945 gathered 143 cases in which complete recovery was reported in 48. Ordinarily cardiac massage was supplemented by the intracardiac injection of adrenalin. The exact duration of the resulting cerebral anoxia compatible with full recovery has however, not been established. Barber and Madden estimated the time limit to be five minutes at the most and more probably between three and four minutes and they pointed out that reports of successful resuscitation after longer periods of cardiac arrest should be evaluated on the basis of the definition of time interval employed. Since re-establishment of circulation begins the moment manual massage is started, they were of the opinion that the duration of cardiac arrest should be defined as the time interval between the cessation of the heartbeat and the performance of manual cardiac massage.²

Greene³ reported one case of cardiac standstill of four minutes' duration occurring during the course of laparotomy. However, in the estimate of duration he included the time taken in massaging the heart and administering artificial respiration which were instituted simultaneously but even so the exact duration of the massage and artificial respiration was not known. If Barber and Madden's definition is adhered to the period of cardiac standstill was overestimated by Greene. The patient passed the first three weeks after resuscitation in a mentally sluggish state after which she recovered completely though retrograde amnesia covering the three week period persisted.

In another instance that of Desmarest and Lhermitte⁴ in which the survival period after cardiac massage was somewhat more than forty eight hours, the cessation of heartbeat was estimated to be of about five minutes. Here also the time spent in massaging the heart and giving artificial respiration was included.

Hawkins, McLaughlin and Daniel⁵ presented a case in which during the course of laparotomy the heart stopped beating for an estimated ten or eleven minutes including seven minutes spent in massaging the heart. tracheal intubation and insufflation of oxygen was instituted at the time of cardiac arrest. Eight days

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- 12 - - - - - icious System New York 1941,
- 13 - - - - - t Rate of the Sympathectomized
- 14 - - - - - of Raynaud's Disease by Resec-
etic Ganglia and Trunks Surg.
- 15 - - - - - the Coronary Circulation, Heart
- 16 Kountz W B, Larson F F and Koenig K F Observations on the Effect of
Flow of the Re-ved Human
- 17 Katz - - - - - Vessels of the Dog Am J
- 18 Master A M, Luzzie - - - - - The Electrocardiogram
and the Two Step Exercise A Test of Cardiac Function and Coronary
Insufficiency Am J M Sc 207 435-450 1944

pleural cavity, the chest was closed and a drain inserted through the seventh interspace in the posterior axillary line. Electrocardiography performed while the patient was still in the operating room disclosed normal cardiac rhythm.

Further Course—During the ensuing days the patient was in fairly good physical condition but failed to regain consciousness. He reacted only to painful stimuli. Frequent aspirations of the nasopharynx and trachea were necessary. On April 25, generalized convulsive seizures set in and continued intermittently. His legs were rigid and all reflexes hyperactive. His eyes remained open most of the time. Intravenous injections of plasma and glucose saline solution were given daily. Repeated roentgenograms showed a gradually decreasing cardiac shadow.

The patient's condition remained much the same until about May 21. His temperature, which had remained in the vicinity of 100° F, rose gradually to 104°, the pulse from about 110 to 140 and respirations from about 24 to 40 but the blood pressure stayed within normal limits. He became weaker, lost weight and a roentgenogram taken May 23 showed mottling of both lung fields. Opisthotonos developed. Death occurred on May 28, thirty days after cardiac arrest.

Laboratory Data—Blood count on admission to hospital revealed 4,609,000 erythrocytes per cubic millimeter; the lowest value was 3,090,000 on May 15. Leucocytes varied from 12,000 per cubic millimeter on admission to 22,500 on April 30. Urinalysis disclosed albumin and many leucocytes on several occasions. Blood chemistry studies including estimations of sugar, chlorides and urea nitrogen revealed no deviation from normal.

AUTOPSY OBSERVATIONS

Gross Examination—Postmortem examination was commenced twelve hours after death. The body was emaciated. The wounds and operative scars were well healed. Both pleural cavities were obliterated by fibrous adhesions. The medial pleural surface was adherent to the pericardium.

The heart together with the adherent pericardium and pleura weighed 600 grams. There was a window in the right pericardium which measured 9.5 by 7.0 cm. The healed wound in the right ventricular wall 2 cm in length extended from a point 1.5 cm beneath the coronary sulcus to 1.0 cm from the lateral border of the ventricle. On cross section the wound was found to extend almost to the endocardial surface where grayish white fibrous tissue measuring 1.5 mm in thickness, separated it from the cavity. The endocardial wall in the vicinity of the wound showed rusty discoloration. Continuous with the lateral border of the wound and extending on to the posterior wall of the ventricle there was a partially necrotized area infiltrated with blood pigment, it measured 3.0 cm in diameter and occupied the entire thickness of the cardiac wall. The right ventricular wall measured from 4 to 6 mm in thickness; the left ventricular wall from 1.5 to 1.8 mm, the tricuspid ring 12 cm in circumference; the pulmonary 6.5 cm; the mitral 9 cm; and the aortic 6.0 cm.

The combined weight of the lungs was 1,450 grams. The cut surfaces were dark red and presented rare granular areas, most prominent in the lower lobes; the largest measuring 1.0 cm in diameter.

The liver weighed 1,500 grams. Except for a few pericapsular fibrous adhesions no changes were observed. The spleen, pancreas, thyroid, adrenal, genitourinary, and gastrointestinal tracts showed nothing remarkable. The kidneys together weighed 350 grams and appeared normal.

The brain after fixation in formalin weighed 1,600 grams. The external surface appeared normal. On multiple section the only change of note consisted of minute hemorrhages in the lower layers of the cerebral cortex and adjacent white matter in the region of the right superior frontal sulcus at the level of the genu of the corpus callosum and in the orbital region of the frontal lobe bilaterally.

Microscopic Examination

Thoracic and abdominal viscera—Sections removed from the region of the heart wound revealed that healing was well in progress. The heart muscle brought into apposition by sutures was joined by scar tissue in which lymphocytes, plasma cells and a varying number

after resuscitation convulsive seizures occurred. Her muscles were hyper-tonic, and there were no voluntary or involuntary movements although she responded to painful stimuli. An electrocardiogram done three days before death showed no abnormalities. The patient survived for twenty-six days without regaining consciousness.

Howkins, McLoughlin and Daniel's case is among the very few in which careful histologic studies have been carried out, therefore, we feel that it is worth while to place on record another instance of temporary cardiac arrest in which survival was sufficiently long to permit the establishment of cerebral changes.

CASE REPORT*

Illness at Time of Admission—The patient, a 29-year-old colored man, was seated in a bar on the evening of April 20, 1946 when in an altercation with a friend, he was stabbed in the chest and face with a pocketknife. He walked about one-half a block to a doctor's office where he collapsed. He remained unconscious for an undetermined period of time, and when he awoke he found himself bandaged. He was brought immediately to hospital by ambulance.

Examination—On admission his pulse was 90 per minute, and blood pressure 105 systolic and 70 diastolic. The site of the wound was in the left third intercostal space 3.0 cm. left of the sternum. A roentgenogram of the chest failed to reveal anything of note.

Course—The following day (April 21) the patient's temperature rose to about 100° F. and penicillin therapy 20,000 units every three hours, was begun. In the afternoon a continuous, aching pain developed in the epigastric region and nausea occurred. The pain was aggravated by coughing. Another roentgenogram failed to reveal effusion in the pericardial or pleural cavities.

Except for a slight elevation in temperature his condition remained satisfactory during the ensuing days. On April 25 roentgenograms taken from the lateral view disclosed a knife blade in the region of the right ventricular wall, which under fluoroscopy was seen to pulsate in unison with the heart. The heart shadow was enlarged and there was evidence of a small amount of fluid in the pericardial and left pleural cavities.

Emergency operation was scheduled for April 26 and in the meantime the patient's blood pressure and pulse were checked every twenty minutes and were found to be within normal limits. Later pericardium

the heartbeat which was felt against the needle, suddenly stopped. A small amount of blood was removed from the pericardial space. The heart was found to be in complete arrest. As a consequence of manual massage and injection of 10 cc. of adrenalin into the heart cavity (during which time the patient received oxygen by insufflation) normal cardiac rhythm was restored. The cubital vein was exposed and a transfusion of 2,500 cc. of blood given. The patient's blood pressure soon returned to normal. The duration of complete cardiac arrest was estimated to have been from three to five minutes.

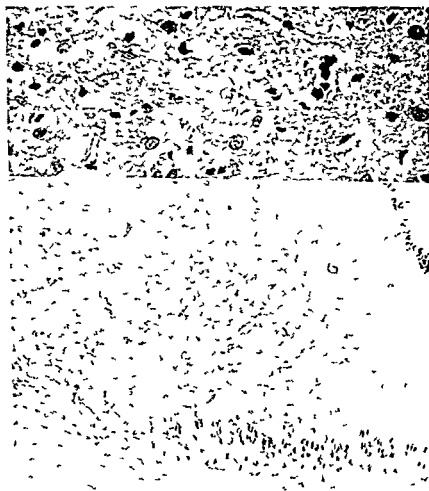
The knife blade was found in the base of the right

sterile saline solution and left open. All fluids were

Brain Many blocks from the brain including every gyrus were removed, so that a study of the topographic distribution of the lesions could be made. The blocks were embedded in paraffin and celloidin and sections were stained by hematoxylin eosin cresyl violet and by the Weil myelin sheath and the Holzer glia fiber methods. Frozen sections from additional representative blocks were stained by oil red O and by the Hortega method for microglia.

The leptomeninges showed little of note aside from puffy thickening of arachnoidal membranes. Not a single section of cerebral cortex was intact but the pathologic changes varied in degree in the different areas. Generally there was a diffuse or patchy reduction of nerve cell with lamina III bearing the brunt of the attack (Fig 1, f). Many remaining nerve cells were shrunken and their nuclei and cytoplasm hyperchromatic. Also there was a dif-

A



B

Fig. 1.—In A, from lamina III of the calcarine cortex, astrocytes are in great profusion (X400, hematoxylin-eosin stain). In B, the hippocampus is shown where there is complete disappearance of granule cell from Sommer's sector with replacement by swarms of microglia. Scattered proliferated astrocytes also are present. The dentate gyrus (in the upper right corner) is focally degenerated (X6, cresyl violet stain).

of pigment containing macrophages were present. In one section, newly formed cartilage and bone were found in the heart muscle adjacent to the wound. The endocardial tissue displayed fibrous thickening, and the endocardial surface was covered by clotted material. Sections from the wall of the heart beneath the posterior leaflet of the tricuspid valve showed necrosis of heart muscle, hemorrhages, and numerous neutrophilic leukocytes. In other sections from the right ventricular wall the interstitial tissue was edematous and contained a few lymphocytes. The epicardium was edematous and fibrous and contained a moderate number of lymphocytes.

The lungs were the seat of bronchopneumonia. As to the liver, its cells had granular cytoplasm and some of the nuclei were enlarged and hyperchromatic. No fatty infiltration was present. The pleura, pancreas, kidneys, and adrenal glands showed nothing remarkable.

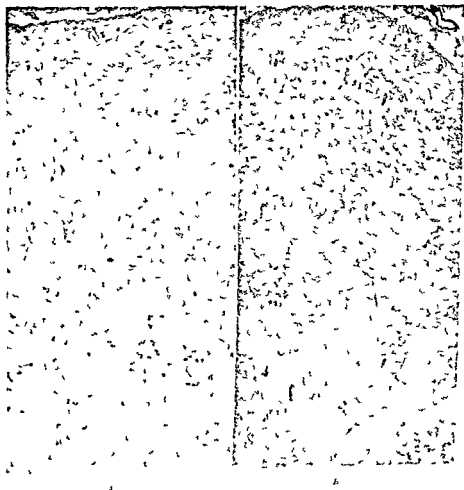


Fig. 1.—In A from the pericalcarine cortex there is a general reduction of ganglion cells. Most of the ganglion cells in lamina III and IV are hyperchromatic (X) in B. The calcarine cortex. Lamination has been lost. Only three or four large ganglion cells

Brain Many blocks from the brain including every gyrus were removed so that a study of the topographic distribution of the lesions could be made. The blocks were embedded in paraffin and sections were stained by hematoxylin-eosin, cresyl violet and by the Weidmeyer method and the Holzer glia fiber methods. Frozen sections from additional representative blocks were stained by oil red O and by the Hergert method for microglia.

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A



B

Fig. —In A, section III of the calcarine to tentorium area in great proportion (X400 in cresyl violet stain). In B the hippocampus is shown there is complete appearance of small cell from Sommer's sector with replacement by swarms of microglia. Scattered proliferated astrocytes also are present. The dentate gyrus (in the upper right corner) is focally infiltrated (X400 in cresyl violet stain).

fuse proliferation of glial cells, particularly microglia and astrocytes in affected areas astrocytes were

As mentioned, the and adjacent cortex (are conspicuous. In area 17 there was a relatively large area bilaterally (about 1.0 cm of cortex on each side) in which the laminae were largely replaced by proliferated glia (Fig 1 B),

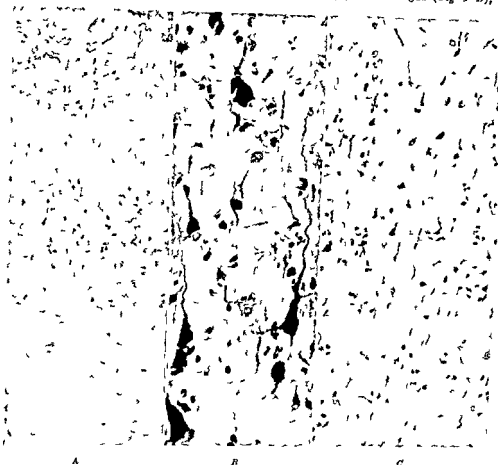


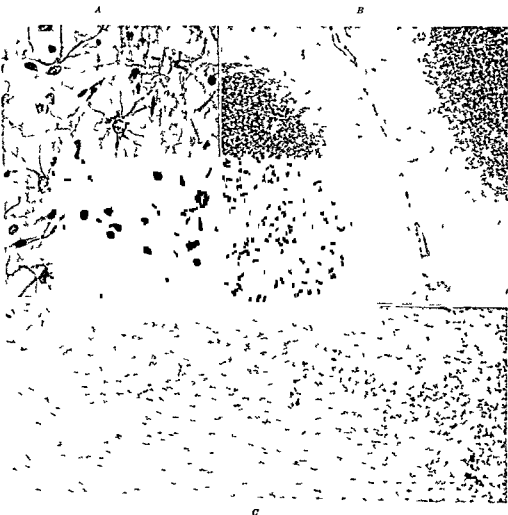
Fig 3
replacement
ganglion cell
(X275 cresyl
visible in the
(X160)

cells with
chromatic
microglia
O fat is
pigment cells

mainly swollen astrocytes (Fig 2 A) and microglia. Furthermore Sommer's sector of the hippocampus was severely damaged only a few nerve cells remaining and astrocytes were in great profusion (Fig 2 B). The dentate gyrus also showed foci of degeneration (Fig 2 B). As to vessels in the cerebral cortex slight vascular engorgement was noted but there was no endothelial or adventitial proliferation. Edema was inconspicuous. Corresponding to the hemorrhagic areas in the frontal lobes noted on gross inspection there were a number of dilated and engorged vessels but no hemorrhages. The vessels probably were pre-existent venous malformations. The cortex adjacent to these vessels showed changes similar to those in the calcarine area except that they were less severe (Fig 3 A). As elsewhere

many remaining nerve cells showed degenerative changes including corkscrewlike deformation of apical dendrites (Fig 3 B). Oil red O stained sections showed fat in moderate numbers of microglia and in many of the remaining nerve cells (Fig 3, C), a finding most striking in Sommer's sector of the hippocampus.

The subcortical white matter displayed only a generalized slight to moderate increase in oligodendroglia and a scattering of rod cells, no demyelination was observed. The same minor changes were apparent in the corpus callosum, the anterior and posterior commissures, the optic tracts, and the internal capsule. On the other hand, the intrahypothalamic part of the fornix showed a pronounced proliferation of oligodendroglia. The subependymal cell plate contained patchy accumulations of microglial cells, generally arranged parallel to the ventricular wall. The ependymal lining of the ventricles was intact except for occasional small granulations of the wall of the third ventricle. A few vessels of the choroid plexuses were fibrous and thickened.



C

Fig 4—A From the pulvinar of the thalamus showing conversion of parenchyma into spongy state with proliferation of astrocytes ($\times 59$ Holzer stain). In B from cerebellar folia, all Purkinje cells have disappeared and cells of the Bergmann layer have increased in number ($\times 100$). In C from the dentate nucleus very few ganglion cells remain and there is diffuse microglial replacement ($\times 90$ cresyl violet stain).

Examination of sections from the basal ganglia disclosed that the most striking changes were in the thalamus. All the thalamic nuclei were equally affected except those most ventrally situated, which were virtually free from change. Many nerve cells had been replaced by a loose glial scar (Fig. 4, A), and numerous remaining nerve cells showed evidence of disintegration. Satellite cells and neuronophagia were occasionally observed, and there were scattered glioses. Vessels showed hyaline or fibrous thickening of the intima, and some were calcified and surrounded by glial scar tissue in which calcified bodies were scattered in the perivascular spaces and parenchyma; there were occasional minute hemorrhages and a few large mononuclear cells and macrophages. In the caudate nucleus and putamen there was also severe loss of nerve cells with corresponding proliferation of rod cells and astrocytes. Scattered satellite cells were present and there were many glioses. The globus pallidus was much less severely affected. The claustrum displayed a moderate loss of nerve cells and sparse proliferation of rod cells.

In sections from the substantia perforata anterior and amygdala little alteration of nerve cells and only slight proliferation of microglia were observed. The nucleus basalis was intact except for a altered rod cells and occasional neuronophagia. In the hypothalamus a few nerve cells were pyknotic, there was considerable microgliosis of the nuclei tuberculi laterales, slight proliferation of microglia in the supraoptic, ventromedial and posterior hypothalamic nuclei and in the mammillary bodies and only occasional microglia in the lateral hypothalamic nucleus.

The medial geniculate body showed considerable loss of nerve cells and a corresponding increase in microglia and astrocytes to almost the same degree in fact as the thalamus. The lateral geniculate body was somewhat less affected. The substantia nigra and basis pedunculi were virtually intact. In the red nucleus and superior colliculi scattered neuronophagia was observed and a light to moderate number of nerve cells displayed chemical changes. Occasional cells of the oculomotor and trochlear nuclei were shrunken, while a few others were swollen and had peripherally displaced nuclei. Occasional microglial cells were seen. The nuclei of the basilar pontis had somewhat less than the usual complement of nerve cells, and there was slight focal and diffuse increase in glia. The remaining pontile nuclei were relatively normal except for apparent ischemic changes.

The medulla oblongata showed a slight diffuse proliferation of oligodendroglia and microglia. A few small perivascular hemorrhages were present in the floor of the fourth ventricle.

The sections from the cerebellum exhibited almost complete loss of Purkinje cells and moderate proliferation of cells of the Bergmann layer (Fig. 4, B). The dentate nucleus displayed severe loss of nerve cells and replacement by countless glia of all categories, particularly microglia (Fig. 4, C).

Spinal cord. One section from the uppermost cervical cord showed nothing of significance.

DISCUSSION

The exact duration of the cardiac arrest is not known but was estimated by the attending surgeon to be between three and five minutes. As to the period of cerebral hypoxia it doubtless was longer if one takes into consideration the preliminary fall in blood pressure and the time required after the beginning of manual massage of the heart for complete re-establishment of the circulation, however these may be regarded as factors of little import if one accepts the conclusion of Hill¹¹ that a mere trickle of blood through the brain serves to maintain life in nerve cells. From the data in our case which were very similar to those of Howkins, McLaughlin and Daniel¹² as regards time interval symptoms and histologic findings it would seem that the maximum period of cardiac arrest compatible with full recovery is less than five minutes.

The most striking symptom in our case was permanent unconsciousness and, as might be expected the cerebral cortex was severely damaged. The whole of the calcarine cortex patchy areas in the middle frontal gyrus and Sommer's sector of the hippocampus bore the brunt of the attack. All other parts of the cortex were also affected and to about an equal degree, except for the precentral gyrus which were somewhat more affected than contiguous parts of the frontal and parietal lobes.

The striking vulnerability of cerebral cortex in stagnant anoxia has been well established in experimental animals as Grenell⁹ has brought out in his recent review of the subject. Following occlusion of the pulmonary arteries of cats for varying periods of time Weinberger, Gibbon and Gibbon¹⁴ found no adverse effects if circulatory arrest lasted no longer than three minutes and ten seconds but if the period was longer the animals exhibited loss of vision motor disturbances abnormal behavior and stupor. Laminae III and IV of the cortex were the most affected. Impaired vision and hearing were noted by Windle and Becker¹⁵ in guinea pigs in which asphyxia neonatorum had been produced by temporarily clamping the umbilical cords in late fetal life but histologic examination of the brains failed to reveal a prevalence of lesions in the visual cortex. Cilder and Cobb occluded the vertebral and the subclavian arteries in cats for varying periods of time and found devastated cortical areas in which the pyramidal cells in lamina V seemed most affected. In similar experiments in cats Gomez and Pike observed that the small pyramidal cells of the cortex were the most sensitive but they did not mention relative laminar vulnerability. Furthermore Grenell⁹ observed in dogs in which the cerebral circulation was completely arrested by means of a cervical pressure cuff (after preliminary removal of the spine and laminae of the second cervical vertebra so that the vertebral and spinal arteries could be compressed) that damage to cortical nerve cells particularly in laminae III and IV occurred in as short a time as two minutes after circulatory arrest. In our case pyramidal cells in laminae III suffered most except in the precentral gyrus where large Betz cells had also disappeared. The most devastated area in the brain was the calcarine cortex (area 17 of Prodmann) where only laminae I, II and VI could still be recognized. This was true also in the case reported by Hawkins, McLaughlin and Daniel¹² who remarked that 'The findings of many investigators have been that the occipital cortex suffers severely and early in cerebral anoxia. Desmarest and Lhermitte⁴ also noted their case of somewhat more than forty eight hours' survival that the visual cortex was severely affected. In Nielsen and Sanborn's case damage to the occipital lobe was restricted to areas 18 and 19 unilaterally. In this connection it may be mentioned that visual disturbances may be encountered in nonfatal cases of anoxia. Parker¹ referred to two cases in this category. One concerned a 4 year old boy who during appendectomy suffered a sudden cardiac and respiratory arrest for several minutes but was revived by the intracardiac administration of adrenalin. Postoperatively he was blind but as time went on a moderate degree of vision was restored. The other instance

was that of a 4 year old girl who during operation for Pecquet's ductus, had cardiac arrest for eight minutes. During the ensuing three weeks she was completely blind, but *five weeks later she could see very large objects enough to avoid them, but could not recognize them as such.* Months later the visual disturbance was still severe.

The advanced destruction of the thalamus and striatum was in conformity with the observations of Howkins and associates though Desmarest and Lhermitte⁴ found that of the two structures, the thalamus was most affected. The *globus pallidus* on the other hand, was little involved, as is often the case in stagnant anoxia.

Another severely affected part of the brain was the cerebellum particularly the dentate nucleus. The observation that many Purkinje cells had disappeared is in accord with the findings of Howkins and co workers Gomez and Pike,⁷ Weinberger, Gibbon, and Gibbon,¹¹ and Grenell,⁹ and at variance with that of Windle, Becker, and Weil,¹⁶ who presented evidence that Purkinje cells have a remarkable recuperative capacity. As to the hypothalamus, its nerve cells were intact although some displayed ischemic changes, and in some nuclei there were proliferated microglia. Such an observation is in line with the acknowledged relative immunity of the hypothalamus to anoxic insult even the histotoxic anoxia produced by cyanide (Ginzler and associates⁶) though Grenell and Kabat¹⁰ noted severe damage to hypothalamic nuclei (supraoptic, paraventricular, and lateral mammillary nuclei excluded) in dogs subjected to cerebral circulatory arrest for nineteen minutes or more.

In attempting to assess the comparative severity of the lesions in the central nervous system as a whole, the following conclusions were reached: damage was *severe* in the cerebral cortex (especially the calcarine area), thalamus (except its ventral part), striatum, cerebellum, and medial geniculate body, *moderate* in the lateral geniculate body, *mild* in the globus pallidus, claustrum, hypothalamus, and red nucleus, and *virtually absent* in the substantia perforata anterior, amygdala, subthalamus, substantia nigra, pons, medulla oblongata, and uppermost spinal cord. The white matter as a whole was well preserved.

Of especial interest were the countless microglia pervading the cerebrum even in areas in which little cell damage could be detected. It seemed that the microglial response was out of proportion to the degree of nerve cell damage. Comparable in this respect was the observation of Windle, Becker, and Weil¹⁶ in the guinea pigs already referred to that swarms of microglia appeared 2½ days after asphyxiation emerging from the ependymal region of the lateral recess of the fourth ventricle and the anterior horns of the lateral ventricles. At the end of one week they had invaded diffusely and indiscriminately the entire brain and after three to four weeks had disappeared. In our case no evidence as to their origin could be found although they were fairly numerous in certain parts of the subependymal cell plate.

The precipitating cause of death in our case was regarded as pneumonia. Throughout the course the heart showed no evidence of decompensation al-

though sinus tachycardia persisted. Histologic examination of the heart revealed that healing was well in progress.

SUMMARY

A man stabbed in the heart was found six days later to have pericardial hemorrhage. During pericentesis the heart stopped beating. The pericardial cavity was hastily opened, the heart massaged, and adrenalin injected, whereupon the heart began again to beat. It is estimated that the cardiac arrest lasted from three to five minutes. The patient survived for thirty days thereafter, the longest thus far recorded in such cases. He remained unconscious during the entire time.

Post mortem examination disclosed severe changes in the brain which consisted mainly of disappearance and degeneration of ganglion cells and replacement by myriad microglia and a smaller number of astrocytes. The cerebral cortex was a site of predilection with the calcarine cortex bearing the brunt of the attack, an observation which bears re-emphasis in view of the potential visual disturbance after nonfatal anoxia. Other severely affected structures were Sommer's sector of the hippocampus, thalamus, striatum, cerebellum, and medial geniculate body. The white matter of the cerebrum was virtually spared.

REFERENCES

- 1 Baker A B. Personal communication to the authors.
- 2 Barber R F and Madden J L. Resuscitation of the Heart. *Am J Surg* 64: 151-168, 1944.
- 3 Barber R F and Madden J L. Historical Aspects of Cardiac Resuscitation. *Am J Surg* 70: 135-136, 1945.
- 4 De May F. and Thomas J. *Am J Surg* 64: 151-168, 1944.
- 5 G. *Am J Surg* 64: 151-168, 1944.
- 6 Cinzler A, Haymaker W, Bodansky O and Ferguson R L. In preparation.
- 7 Gomez L and Pike F H. The Histological Changes in Nerve Cells Due to Total Temporary Anemia of the Central Nervous System. *J Exper Med* 11: 257-265, 1909.
- 8 Greene F H. *Am J Surg* 64: 151-168, 1944.
- 9 Grenell E G. *Am J Surg* 64: 151-168, 1944.
- 10 Grenell E G, and Kabat H J. Central Nervous System Resistance. II. Lack of Correlation Between Vascularity and Resistance to Circulatory Arrest in Hypothalamic Nuclei. *J Neuropath & Exper Neurol* 6: 35-43, 1947.
- 11 Hill L. On Cerebral Anemia and the Effects Which Follow Ligation of the Cerebral Arteries. *Phil Tr Roy Soc B* 193: 69-122, 1900.
- 12 Howkins J, McLaughlin, C R and Daniel, I. Neuronal Damage From Temporary Cardiac Arrest. *Lancet* 1: 488-490, 1946.
- 13 Nielsen J M, and Sanborn A L. Visual Agnosia for Animated Objects. *Bull Los Angeles Neurol Soc* 7: 102-104, 1942.
- 14 Weinberger L M, Gibbon M H and Gibbon J H Jr. Temporary Arrest of the Circulation to the Central Nervous System. Physiologic Effects. *Arch Neurol & Psychiat* 43: 615-634, 1940.
- 15 Windle W F and Becker R F. Asphyxia Neonatorum. An Experimental Study in the Guinea Pig. *Am J Obst & Gynec* 45: 183-200, 1943.
- 16 Windle W F, Becker R F and Weil, A. Alterations in Brain Structure After Asphyxiation at Birth. An Experimental Study in the Guinea Pig. *J Neuropath & Exper Neurol* 3: 224-239, 1944.

TENSION ON THE SUTURE LINE IN PERIPHERAL NERVE SURGERY

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THE maxim that tension shall not be placed on the suture line in a neurorrhaphy has been generally accepted. This follows the general principle of surgery that sutures shall be placed without tension wherever possible. That serious consequences will follow the use of tension in neurorrhaphy has been stated unequivocally, or implied indirectly, by many authors.^{1,4} In contradistinction Frazier⁵ and Sanders⁶ considered that slight tension was not certainly harmful. Whether suture without tension is or is not desirable its performance is frequently extremely difficult or even impossible with the large nerve gaps resulting from the wounds of modern war or industrial and traffic accidents. Even with the methods of nerve transplantation and joint positioning at our disposal, it is frequently impossible to approximate the nerve ends without tension.⁷ The results of the massive dissections or bone resections for extremity shortening to obtain nerve length⁸ may be as disabling as the nerve injury itself.⁹ Staged procedures if properly utilized result in a decrease in the ultimate tension. Since nerve grafts for the large major nerves have in general given unsatisfactory results^{10,11} although more recently Seddon¹² and Holmes¹³ have indicated that better results may be expected, the most satisfactory method for obtaining reinnervation remains nerve suture with or without tension.

The purpose of the present study was to determine the effects of tension applied to the suture line on the end results of neurorrhaphies in a small group of carefully observed cases. Three hundred three cases or approximately one fifth of the major neurorrhaphies studied, had the necessary information for proper evaluation (Table I). All cases were studied at Wakeman General Hospital and most patients were operated upon at that hospital although cases were included from almost all Army neurosurgical centers.

RESULTS

The 303 cases were divided into two groups. Group 1 includes all those cases followed long enough to observe a final definitive result. Group 2 includes those in which a definitive result could not be established because of (1) insufficient follow up (2) severe associated injuries especially to bones joints or muscles and (3) preoperative function not commensurate with the obvious nerve lesion.¹⁴

When the cases with definitive results (Group 1) are evaluated (Table II) it becomes apparent that in this group the nerves which were repaired under slight to moderate tension had the most satisfactory final results. As might be expected, none of the nerves sutured with maximum tension had a complete return of function, but many had fair and good results (80.6 per cent). Even

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TABLE I TOTAL NUMBER OF CASES OF EACH NERVE AND NUMBER OF CASES FOR EACH TENSION GROUP*

NERVE	NUMBER OF CASES	PER CENT OF TOTAL CASES	NUMBER WITH TENSION OF				
			0	1	2	3	4
Median	32	17.0	12	3	18	10	3
Ulnar	105	34.7	29	18	34	20	4
Radial	31	16.5	10	9	16	1.2	4
Brachial plexus	6	3					
Musculocutaneous	1		0	4	1	3	1
Axillary	2						
Sciatic	4	14.1	4	7	12	14	5
Tibial	19	6.3	2	5	7	6	4
Peroneal	24	7.3	2	5	7	9	1
Total cases	300		58	54	94	74	22

The musculocutaneous and axillary nerve are included with the brachial plexus for the breakdown by tension in this and all subsequent tables the tension is indicated by figures 0-4 as follows

0 -
1

3

4

approximate the ends

tearing necessary to

In two instances (Cases 1 and 2) even with the maximum tension it was impossible to approximate the ends

TABLE II CASES WITH DEFINITIVE RETURN OF FUNCTION

DEGREE OF RETURN OF FUNCTION	DEGREE OF TENSION									
	0		1		2		3		4	
	NO OF CASES	PER CENT	NO OF CASES	PER CENT	NO OF CASES	PER CENT	NO OF CASES	PER CENT	NO OF CASES	PER CENT
4 Excellent	3	100	5	14	12	18.1	1	1.2	0	0
3 Good	12	60	22	42.9	27	41.5	14	42.4	6	42.5
2 Fair	12	60.7	5	14.3	17	25.7	1	7.7	6	42.5
1 Poor	8	40.0	1	2.9	11	16.6	2	6.0	1	2.2
0 No return	4	100	1	2.9	3	4.3	1	3.0	1	2.2

Return of function indicates function 1 indicates from one element to from 0 per cent to element Tension as number of cases in each

TABLE III CASES WITHOUT DEFINITIVE RETURN OF FUNCTION (GROUP 2)

ESTIMATION OF RETURN OF FUNCTION	DEGREE OF TENSION									
	0		1		2		3		4	
	NO OF CASES	PER CENT	NO OF CASES	PER CENT	NO OF CASES	PER CENT	NO OF CASES	PER CENT	NO OF CASES	PER CENT
Return of function	4	80.0	3	60	6	60	6	60.1	1	80.0
No return of function	3	60	2	40	1	20	4	40	1	13.3
Alleviation of Tinel sign	4	100	44	81.5	33	61.5	70	67.5	10	90
No alleviation of Tinel sign	1	20	1	20	1	20	1	20	1	10

The percentages are on the basis of all cases in each group

in cases where it was impossible to approximate the nerve ends by the use of maximum tension, satisfactory results have been obtained as in Case 1

CASE 1—C B, a soldier, had a neurorrhaphy of the radial nerve at the mid one third of the humerus on March 28, 1945 six months after injury. A large neuroma was excised to reach fair nerve ends. Even with marked tension it was impossible to bring the nerve ends into apposition, and a gap of approximately 3 mm remained at closure. By six months after operation there was return of function of the brachioradialis and supinator muscles and a Tinel sign to 20 cm. Despite this return of function and because of the supposedly unsatisfactory neurorrhaphy, the nerve was reexplored on Oct 2, 1945. A fairly large, irregular neuroma, 2 cm in length was found at the suture site (Fig 1). Stimulation of the nerve both above and below the suture line gave contraction of the brachioradialis supinator extensor carpi radialis and extensor carpi ulnaris muscles. A partial external neurolysis was performed. By the time of discharge, three months after operation there was good voluntary contraction of these muscles plus beginning function of the abductor pollicis longus and extensor pollicis longus and there was beginning return of sensation.



Fig 1 (Case 1)—Photograph at reoperation of the radial nerve sutured under tension of 4 with a gap of approximately 3 mm. Shown partially dissected.

and good results were obtained with an actual return of function actually of excellent 29 per cent and 53.6 per cent, and 42.8 per cent and the highest percentage of poor results and no return of function 30.8 per cent as compared to 8.6 per cent 21.1 per cent 9.0 per cent and 14.4 per cent.

The cases in Group 2 were rated only as showing some return of function, or advance of the Tinel's sign. There is no significant difference in the percentage of cases showing return of function or advance of the Tinel's sign in the various tension groups. However, again the nerves repaired without tension had the lowest percentage of return of function (Table III).

The number of cases in which reoperation was deemed necessary and the findings at reoperation are of some importance in evaluating results following neurotomy (Table IV). All cases with reoperation are briefly reviewed (Table V). In cases with marked tension there was a definite tendency to re-explore early because of the prevailing opinion that with tension failure was assured. In many cases re-exploration was performed as an incidental procedure at the time of operation on other nerves as in Cases 9, 24 and 25, and in other cases only because of the presence of a trigger point, as in Cases 11 and 17.

TABLE IV. CASES WITH REOPERATION AND NUMBER OF CASES WITH VARIOUS TYPES OF PATHOLOGY IN EACH TENSION GROUP

RESULTS OF OPERATION	DEGREE OF TENSION									
	0		1		2		3		4	
	NO OF CASES	PER CENT	NO OF CASES	PER CENT	NO OF CASES	PER CENT	NO OF CASES	PER CENT	NO OF CASES	PER CENT
Reoperated	6	10.1	5	9.1	8	14.3	7	9.4	5	22.7
Separation of the suture line	1	1.7	1	1.8	0	0	2	2.7	2	9.0
Large neuroma	-	-	-	-	-	-	0	-	1	-
Small neuroma	1	-	1	-	1	-	2	-	2	-
Scarring	-	-	0	-	1	-	1	-	0	-
Normal appearance	0	-	1	-	3	-	-	-	0	-

The percentages are computed from the total number of cases in each tension group.

The actual condition of the nerves at reoperation is of significance. As might be expected, there were relatively more cases with separation of the suture line in the groups with high tension. However, even in the group with maximum tension this number is not extreme (two cases or 9 per cent). It is of interest that all separations occurred in those cases repaired with simple epineurial sutures regardless of the type or size of suture material, except in two cases in which the type of suture was not stated (Cases 2, 3, 7, 12, 20 and 27). There was no instance of suture line separation in those cases known to have been repaired with stay sutures in the sheath (See discussion).

All but one of the separations occurred in the peroneal nerve or the peroneal segment of the sciatic nerve (Cases 2, 3, 7, and 27). The remaining case was a partial separation of the median nerve (Case 20).

The presence of neuromas and scarring in the nerve was also recorded. The larger neuromas occurred most frequently in the low tension groups (Fig. 2). The only normal appearing nerves at reoperation were in the groups repaired with slight to moderate tension (tension 1, 2 and 3) and the most normal nerves appeared in the groups with tension of 2 and 3 (Fig. 3).

TABLE V. BRIEF SUMMARY OF NILE CASES WITH REOPERATION

NUM OF CASES	NERVE	LOCATION	TIME IN JURY TO OPERATION (IN MO.)	TENSION	SUTURE MA- TERIAL AND TYPE	RESULT FOR REOPERATION	TIME AFTER FIRST OPERATION (IN MO.)	FINDINGS	OPERATION	RESULT
<i>Cases With Tension of 4</i>										
1	Radial	Med humerus	6	4+	Silk stays (cool and epineural)	Condition of nerve at operation	6	Partial neuroma	Ly is	Good
2	Peroneal	1 of iliac space	10	4	Lantulum epineural	No return	3	Suture line separation straightening knee	2 stage orthophy	No return
3	Sciatic	Mid thigh	5	4	Silk epineural	100% return of function	17	Peroneal separated tibial small neuroma	Orthophy peroneal	Inadequate f u
4	Ulnar	Mid fore arm	1 day	4+	Silk lig (cool)	No return of sensation	4+	Nerve in partial continuity with irregular neuroma	Partial orthophy	Excellent
5	Tibial	Function middle and lower 1/2 of calf	9+	4	Lantulum sling and epineural	No return of sensation	10	Small soft neuroma continuity	Orthophy	Inadequate f u
<i>Cases With Tension of 3</i>										
6	Brachial plexus	Clavicle	3	3	Lantulum sling and epineural	100% return of function	10	Continuity scarred	Ly is	Inadequate f u
7	Peroneal common fibula	1 of iliac space	7	3	Silk epineural	Poor result	5 1/2	Separation 7.5 cm	Orthophy 2 stage	Poor
8	Peroneal	1 of iliac	11	3	Silk stay of epineural	No motor return	5	Continuity	Orthophy	Inadequate f u

9	Median radial ulnar and cu taneous	Axilla	1	3	Silk stay epineural	Inefficient time	on stage in ulcer throphy in ulnar nerve	1	Suture line could not be dis- tinguished from normal nerve	Orbital hy ulnar	ulnar o Tinel's sign In a leguate f u
10	Scapula	Upper 2/3 of thigh	1		Silk stay epineural	Position and ad- hesion of Tinel's sign	Cultivation at first operation	5	Nerve scarred greatly length of suture line could not be disting- uished	1 year	In a leguate f u
11	Median and ulnar	Mid 1/3 of arm	1 1/2	3	Entalium along and lateral lum foil	Fair Poor	Causation and trig- ger point	7	Small neu- roma Large neu- roma roma	Full re- flexion 100% re- covery	Recovery after 9 mo for trigger point good reult in lum poor re- sult ulnar
12	Scapula	Mid 1/3 of thigh	4 1/2	3	Silk epi- neural	Good tibial nerve turn peroneal	No return peroneal	17	Large neu- roma of tibial separa- tion per oneal 7 cm	1 year	Good Poor
Cases With Lesion of 2											
13	Median and ulnar	Upper 2/3 of arm	2	-	Unknown	Good No return	100% result ulnar	1	Both intact ulnar scarred	1 year	In a leguate f u
14	Radial	Lower 1/3 of arm	1	-	Unknown	Fair	No am- prove- ment after 6 mo	1	Large neu- roma	1 year	In a leguate f u

TABLE 3. BRIEF SUMMARY OF ALL CASES WITH REOPERATION

NUMBER	NERVE	POSITION	TIME IN JURY TO OPERATION (IN MO)	TENSION	SUTTER MATERIAL AND TYPE	RESULT	REASON FOR REOPERATION	TIME AFTER FIRST OPERATION (IN MO)	FINDINGS	OPERATION	RESULT
<i>Cases With Tension of 4</i>											
1	Radial	Mid humerus	6	4+ Separ 3 mm	Silk stays and epineural	Cool	Constriction of nerve at operation	6	Large neuroma	Lysis	Cool
2	Cronal	Epilateral epa 6	10	4	Tantalum epineural	No return	Suture line separation straightening knee	3	Separation 5 cm	- stage orthophy	No return
3	Median	Mid thigh	3	4	Silk epa neural	Good	Good return of function	17	1 cronal separated tibial small neuroma	Orthophy peroneal	Inadequate f u
4	Ulnar	Mid fore arm	1 day	4+ Separ 1 cm	Silk ling blood	Good	No return of sensation	4+	Nerve in continuity with irregular neuroma	1 arterial orthophy	Excellent
5	Tibial	Junction middle and lower 1/3 of calf	9+	4	Tantalum sling and epineural	Good	No return of sensation	10	Small soft neuroma continuity	Orthophy	Inadequate f u
<i>Cases With Tension of 3</i>											
6	Brachial plexus	Clavicle	3	3	Tantalum sling and epineural	Good	Good return of function	13	Continuity scarring	Lysis	Inadequate f u
7	Cronal	Head of humerus	1	3	Silk epa neural	Good	Good return of function	5 1/2	Separation 7.5 cm	Orthophy 2 stage	Poor
8	Peroneal	1/3 thigh	11	3	Silk stay epineural	No return	No motor return	8	Continuity	Orthophy	Inadequate f u

	Ulnar	Lower $\frac{1}{2}$ of arm	1	1	Tantalum sling epineural	No return	No return	Orriaphy	Good
	Ulnar	Mid fore arm	7	1	Silk stays in sheath epineural	No return	2nd stage on m. li an nerve	Intact with small neuroma	1 air inside quato fu
<i>Cases With Tension of 0</i>									
23	Median and Ulnar	Axilla	1	0	Tantalum wire epineural and foil cuff	No return	Neuror raphy Radial nerve	Intact without neuroma Narrow inc, disc to foil	Irregular fu but begin ning re turn function
24	Ulnar	Wrist	-	0	Fine silk	Unknown	Neurolysis	Diffuse hard neuroma	Good
25	Ulnar	Lower $\frac{1}{4}$ of arm	1	0	Silk stays in sheath epineural	100%	Slow return function	Small soft neuroma	Fair to good
26	Ulnar	Upper $\frac{1}{2}$ of fore arm	100%	0	Tantalum	100%	Tricker point	Large hard neuroma	Good
27	Peroneal	Optical space	6	0	Unknown	No return	No return	Partial almost complete separation	Separation suture line 3rd near orriaphy without return function
28	Radial	Lower $\frac{1}{2}$ of arm	3	0	Tantalum and cotton	Fair	No im prove ment in 6 months	Scarring moderate	No return

TABLE V—CONT'D

NLM SER	NERVE	POSITION	TIME IN JURY TO OPERATION (IN MO.)	TENSION	SUTURE MA- TERIAL AND TYPE	RESULT	REASON FOR REOPERATION	TIME AFTER FIRST OPERATION (IN MO.)	FINDINGS	OPERATION	RESULT
15	Peroneal	Lower $\frac{1}{4}$ of thigh	6	-	Silk cat neural	No return	No return	6	Large neu- roma	Orriaphy	Inadequate fu but begin- ning sen- sory re- turn and Tinel's sign
16	Sciatic	Upper $\frac{1}{4}$ of thigh	3 1/2	-	Silk stay epineural tantalum	1 air	Return not considered sat- isfactory	13	Small neu- roma	Lysis	Good
17	Ulnar	Lower $\frac{1}{4}$ of arm	3	-	Tantalum wire tantalum foil cuff	1 air but trigger point	Trigger point	13	Suture line could not be iden- tified	Removal fool	Good
18	Ulnar	Mid $\frac{1}{4}$ of arm	1 1/2	-	Unknown	No return	No return	11	Suture intact without neuroma	Lysis	Inadequate fu
19	Peroneal	1 (lateral) space	5	-	Unknown	Tinel's had sensory return	No motor function	16	Hard neu- roma	Lysis	No further return
20	Median	-	1	1	Tantalum wire cotton epineural	Fair	No recent improve- ment	-	Partial separa- tion	Partial orriaphy	Excellent

Cases With Tension of 1

In reviewing the cases it seems apparent that better results might have been expected if more two stage procedures had been used in the maximum tension group.

Another factor which may affect the result is the suture material and the type of sutures used. Silk sutures were used most frequently in the cases in this series especially those treated at Wakemán General Hospital. Sling sutures, through the nerve substance were used rarely. The procedure of

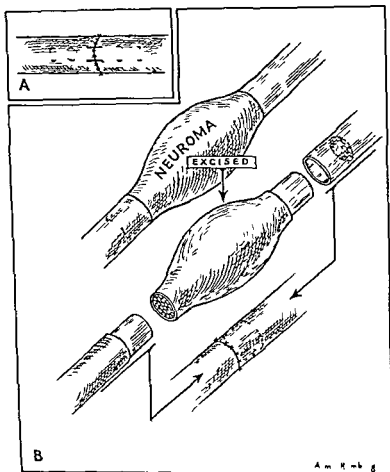


Fig. 4.—A. Drawing to illustrate the method used to place stay sutures in the nerve sheath in cases with marked tension. B. Drawing to illustrate suture as performed with the direct suture with a cuff.

choice in nerves under tension was considered to be the use of stay sutures of silk usually 0 or 00 silk in the sheath. These stay sutures were placed as shown (Fig. 4 A) with the tension applied at some distance from the end of the nerve. With less tension simple mattress sutures or interrupted sutures of 0 silk in the sheath placed away from the nerve end were used as stay sutures. The sheath was then approximated using 000000 silk either as inter

OTHER FACTORS CONSIDERED

It is well recognized that many other factors beside tension affect the end result in nerve repair. Most of these were considered in this study and were found to be essentially equalized in the various groups. Under similar conditions of repair, the radial, median and sciatic nerves will give more satisfactory results than the ulnar, tibial and peroneal nerves. It will be noted (Table VI) that the number of satisfactory and unsatisfactory result nerves are practically identical in each tension group.



Fig 2

Fig 2 (Case 2) —Ulnar nerve with small cauliflower neuroma at suture site two months after neurorrhaphy.



Fig 3

Fig 3 (Case 3) —Median nerve at reoperation, three months after neurorrhaphy with a tension of 2. Note the smooth contour without evidence of a separation or neuroma formation.

The use of multiple stage procedures will be a factor in the result of nerve repair. As would be expected, two stage procedures were used most frequently in the nerves with the largest gaps and so the greatest tension. Thus in the groups with tension of 2, 3 and 4 the relative frequency of one stage to two stage procedures was respectively 5:1, 3:1 and 8:1 while in the groups with tension of 0 and 1 the relative frequency in both was 18:1.

blood supply for a long section of nerve may be lost without seriously affecting the result.^{1 16 17} a similar loss may be an important factor in the results following repair of nerves under tension. This is not dissimilar to the results of nerve damage associated with the use of a tourniquet where it was found that an injury which would not cause paralysis with normal circulation would cause paralysis if the blood supply were cut off by a tourniquet.^{18 19} A limited exposure of the nerve will prevent serious vascular damage in most instances. Dissection of the nerve for long distances probably enables one to place less tension on the suture line but there will be more vascular damage and in addition, the nerve will become fixed by scar tissue which will prevent stretching of the nerve and place increased tension on the short, uninvolved portion of nerve. With a limited exposure a shorter section of nerve is fixed by scar leaving a longer segment of relatively normal nerve to stretch in a smooth undivided sheath.

Another factor which may affect the result in any neurorrhaphy is the relative position of the injury on the nerve trunk. Suture lines at or near the midpoint of the nerve are much more amenable to tension than those at either end especially those near the proximal end. The tension will be the same on both sides of the suture line and this will cause greater relative stretch on the short than on the long limb. It is well recognized that the nerve roots will not stand as much tension as will the distal trunk. This fact is of great importance in high sciatic and brachial plexus injuries. Inequalities in length at the distal end may well explain the poor results in peroneal neurorrhaphies as there is a very short trunk with sharp angulation between the branching of the sciatic and the multiple terminal motor branches of the peroneal.

The length of time of fixation and the method of straightening flexed joints has varied markedly from one group of nerve surgeons to another. It has been considered and proved experimentally that the suture line is as strong after two to three weeks as it will become.² Whether the joint is to be extended gradually by a controlled method such as a turnbuckle cast, or by the patient himself has been the main subject of dispute. In the majority of the cases in this series the extremities were kept in the position of choice by casts or splints for two to three weeks depending upon the tension on the nerve and then they were gradually extended by regulated exercises over a period of two to four weeks.

DISCUSSION

Although it has been considered that tension should not be placed on the suture line there are some theoretical and experimental factors in favor of placing at least minimal tension on the suture line. If the nerve is completely lax the nerve fibrils may buckle causing them to grow laterally or in a direction other than downward into the distal trunk.¹ Weiss² in his discussion of the plasma clot method of suture mentioned as one of the advantages of this method the tendency of the nerve to retract putting the fibrin strands of the plasma clot on a stretch and giving the nerve fibrils a straight path

TABLE VI NUMBER OF POOR AND GOOD RESULT NERVES IN EACH TENSION GROUP

TENSION	SATISFACTORY NERVES (RADIAL MEDIAN SCIATIC)		UNSATISFACTORY NERVES (TIBIAL, PEROXAL ULNAR)	
	NO OF CASES	PER CENT	NO OF CASES	PER CENT
0	26		33	
1	25		25	
2	4		46	
3	3		36	
4	9		12	
Total cases	142		152	

rupted sutures or as a continuous suture. These sutures were placed so as to evert the sheath and leave a smooth closure with the least possible gap for scar tissue to enter. An apparently more desirable procedure was carried out in a few cases. An elongated cuff was made from the sheath at one end, usually the proximal, while a similar length of nerve was denuded of sheath at the opposite end, and the sheaths were then sutured at a point distant from the point of contact of the nerve fibrils (Fig 4 B). This method should leave the nerve fibrils at their point of contact ideally situated according to the criteria of Weiss,²² in a normal sheath with a slight gap filled with serum, separating their ends.

The condition of the nerve ends at the time of suture was considered of such importance that frozen section was done on as many cases as possible at Wakeman General Hospital. The number of cases in which the condition of the nerve is recorded is so small (102) as to be of doubtful significance. In almost all the cases studied the nerve ends were fair or good and the percentage of each type in the different groups was essentially the same except in the group with a tension of 3 (Table VII).

TABLE VII CASES IN WHICH FROZEN SECTIONS WERE PERFORMED

CONDITION OF NERVE		DEGREE OF TENSION									
		0		1		2		3		4	
		NO OF CASES	PER CENT	NO OF CASES	PER CENT	NO OF CASES	PER CENT	NO OF CASES	PER CENT	NO OF CASES	PER CENT
Poor	A	0		1	11.7	1	3.6	8	41.2	0	
Fair	B	5	33.3	5	29.4	10	35.7	16	45.5	3	33.33
Good	C	10	66.6	10	58.8	17	60.7	9	27.3	6	66.66
Normal	D	0		0		0		0		0	

— = no nerve and the tension used. The percentages are D

The damage to other tissues including muscles tendons and bones as well as vascular injury and joint involvement were evaluated and no significant difference was found in the five tension groups.

The vascular supply of the nerve may affect the result in neurotaphy. Although it has been shown that in ordinary nerve dissections the external

blood supply for a long section of nerve may be lost, without seriously affecting the result.^{1, 16, 17} A similar loss may be an important factor in the results following repair of nerves under tension. This is not dissimilar to the results of nerve damage associated with the use of a tourniquet, where it was found that an injury which would not cause paralysis with normal circulation would cause paralysis if the blood supply were cut off by a tourniquet.^{18, 19} A limited exposure of the nerve will prevent serious vascular damage in most instances. Dissection of the nerve for long distances probably enables one to place less tension on the suture line but there will be more vascular damage and, in addition the nerve will become fixed by scar tissue which will prevent stretching of the nerve and place increased tension on the short, uninvolved portion of nerve. With a limited exposure a shorter section of nerve is fixed by scar, leaving a longer segment of relatively normal nerve to stretch in a smooth undissected sheath.

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DISCUSSION

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into the distal stump. The same should hold true with a suture line under tension the epineurium being in close approximation with the nerve fibrils tending to pull apart in a serum blood clot.

It has been suggested that even if the suture line holds the tension on the nerve itself will result in irreparable damage, because of tearing of nerve fibrils and hemorrhage.^{1, 2} By experiment, this has been more or less disproved. Denny³ showed on the intact nerve that hemorrhage occurred rarely, only with extreme tension and that the first structure to give way was the sheath rather than the nerve fibrils themselves. With marked tension there was beading of the nerve fibrils, but no actual tear. Even with a stretch sufficient to increase the nerve length 100 per cent there was paralysis beginning twenty four hours after the injury but complete return of function within two months. Takimoto⁴ showed that a tension equivalent to a weight of 32 kg was necessary to cause a temporary loss of function. Mitchell⁵ stated that a nerve could be stretched three quarters inch for each two inches of length. Sanders⁶ and Frazier⁷ came to the conclusion (from clinical material) that moderate stretch of the nerve was not too detrimental. Sanders suggested a stretch of 10 per cent of the mobilized length of the nerve might be applied without damage but that 30 per cent might be harmful even if applied in two stages. Frazier stated the maximum stretch should not exceed 7 to 8 cm. Although many of the cases of this series, especially those in the group with a tension of 4 exceeded the 10 per cent or 7 to 8 cm maxima they never approached the tension indicated by the other authors. The following case is of interest in this regard.

CASE 29.—This soldier had a severe guttering wound of the medial side of the ankle and foot. At exploration, the nerve ends were found to be separated by 14 cm and after excision of neuromas the gap was 16 cm. After mobilization of the nerve to the popliteal space it was possible to suture the tibial trunk to the plantar nerves with a tension of 3.0 silk stay sutures and a 000000 silk running lock stitch in the sheath were used. Unfortunately, the patient developed meningitis and succumbed on the fourth postoperative day. ¹ = 1.4 cm. = without evidence
about its length
structure

This case, with its complete pathologic study tends to support the opinion of those who hold that definite tension need not seriously damage a nerve. The end results in this series of cases indicate that this opinion is valid and that, if necessary, one should not hesitate to apply tension in order to approximate the ends of the nerve in neurorrhaphy.

CONCLUSIONS

1 Slight to moderate tension on the suture line in peripheral nerve surgery is not harmful and may be beneficial with proper attention to detail in the repair.

2 Maximum tension although not desirable may result in satisfactory return of function even in the occasional case with a small gap remaining between the nerve ends.

3 Maximum tension on the suture line is probably preferable to a nerve graft in the human being.

4 A method of suture for use in neuroorrhaphy is described. No cases in which this method was used had suture line separation even with maximal tension.

REFERENCES

- 1 Spurling R Glen. Peripheral Nerve Surgery—Technical Considerations J Neuro surg 1 133 148, 1944
- 2 Stookey Byron. Surgical and Mechanical Treatment of Peripheral Nerves Philadelphia 1922 W B Saunders Company pp 103 106
- 3 Pollock Lewis J and Davis Loyal. Peripheral Nerve Injuries New York 1933 Paul B Hoeber, Inc. p 207
- 4 Highet, W B and Holmes W. Traction Injuries to the Lateral Popliteal Nerve and Traction Injuries to the Peripheral Nerves After Suture, Brit J Surg 30 212 233, 1942
- 5 Frazier Charles H. Surgical Problems in the Reconstruction of Peripheral Nerve Injuries Ann Surg 71 110 1920
- 6 Sander F K. The Repair of Large Gaps in the Peripheral Nerves, Brain 65 231 303 1942
- 7 Babcock W W. A Standard Technique for Operations on Peripheral Nerves Surg Gynec & Obst 45 364 38 1947
- 8 Dandy Walter E. A Method of Protecting Nerves Requiring Re-Action J A M A 122 35 36, 1913
- 9 Coleman C C. Surgical Treatment of Peripheral Nerve Injury Surg, Gynec & Obst 78 113 124 1944
- 10 Seddon H J and Holmes W. The Late Condition of Nerve Homografts in Man Surg Gynec & Obst 79 342 361 1944
- 11 Spurling R Glen Lyons W P Whitcomb B B and Woodhall Parnes. The Failure of Whole Autografts Brit J Surg 35 161 173 1944
- 12 Seddon H J. Autografts Brit J Surg 35 161 173 1944
- 13 Holmes W. Autografts Brit J Surg 35 161 173 1944
- 14 Clifton E E. Unusual Innervation of the Intrinsic Muscles of the Hand by Median and Ulnar Nerves SURGERY 23 12 31 1945
- 15 Adam W E. The Blood Supply of Nerves J Anat 77 243 250 1943
- 16 Bentley F H and Schlapp W. Experiments on the Blood Supply of Nerves J Physiol 102 6 1943
- 17 Barsick P and Wyburn G M. Effect of Interference With the Blood Supply on the Regeneration of Peripheral Nerves J Anat 79 74 82 1945
- 18 Speigel I J and Lewin Y. Tourniquet Paralysis J A M A 129 4 24 25 1945
- 19 Denny Brown D and Brenner C. Paralysis of Nerve Induced by Direct Pressure and by Tourniquet Arch Neurol & Psychiat 51 126 1944
- 20 Tarlov I M. How Long Should an Extremity Be Immobilized After Nerve Suture Ann Surg 126 366 375 1947
- 21 Tarlov I M. Autologous Plasma Clot Suture of Nerves, J A M A 126 741 748 1944
- 22 Weiss F. The Technology of Nerve Suture and Related Methods of Nerve Repair J Neurosurg 1 133 148 1944
- 23 Denny Brown D and Doherty. Stretching of Peripheral Nerves Arch Neurol 51 126 1944
- 24 Takimoto B. Leber des Nervend. Untersuchung Mitt d med Fakultät d k.
- 25 Mitchell S W. Injuries of Nerves and Their Consequences Philadelphia 1872 J B Lippincott & Company pp 2 24

SOUL DISABILITIES OF THE KNEE

A STATISTICAL SURVEY

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DISABILITY of the knee joint as the result of disease or injury, is not an uncommon problem presented to the general surgeon. Therefore it is desired to present some clinical data of patients with internal derangement of the knee joint and to indicate the uses of a simple constructed dynamometer as it may be applied in the treatment of such disabilities.

There were 293 patients or 15 per cent of 5467 patients admitted to Oliver General Hospital Augusta Ga. during a period of eleven months in 1943 with disability of the knee joint. These were divided as follows: arthritis 42, synovitis 57, sprain and strain 13, dislocation of patella 2, interstitial calcification about the knee joint 6, psychosomatic disease 17 and internal derangement of the knee joint 146. Of the latter 73 patients not selected for operation were treated conservatively by bed rest, traction, rest, aspiration, graduated physiotherapy and muscle training. In the course of rehabilitation an estimation of the rate of recovery of the quadriceps muscle group and later the weight bearing power of the extremity can be aided by objective muscle power tests.

EVALUATION OF THE EXTENSOR MECHANISM OF THE KNEE A MUSCLE POWER TEST

Correction of pathologic conditions responsible for internal derangement without undue delay is important but equally necessary before secure unlimited function can be obtained. Recovery of lost muscle power and volume which invariably affects the extensor mechanism of an injured knee.^{2, 13} The difficulty in estimating the extent and rate of recovery prompted the invention of a circular scale with a short acting gravity lever (approximately 14 inches) as a dynamometer (Fig. 1) for measuring the power of the quadriceps and associated groups of muscles. In performing the spring scale test the warmth of the leg was determined by palpation and previous measurements of the circumference of the thigh and leg were checked. The tests were not made in the presence of other patients; the patient was unable to observe the recording of the scale and no comments were made except encouragement to produce maximum muscular contraction.

The results of innumerable tests on forty patients during their reconditioning process indicated certain permissible inferences: (1) The maximum extensor strength of the thigh muscles ranges from 50 to 150 pounds. (2) The progress of muscle restoration can be accurately charted by repeated examinations. (3) The response to massage, physical therapy and exercise may be observed by detecting differences of muscle strength at interval re-examinations. (4) Excessive treatment or exercise may be first noticed by failure of increasing muscular power. During periods of inactivity little change and sometimes

rapid diminution in muscle power was recorded. Failure to work or the employment of protection of the extremity by the patient, is reflected by no increase in power. (5) The height and weight of the patient are not significant in determining the power of the quadriceps. (6) Atrophy does not indicate the actual power of the quadriceps extensor group. Increment in muscle strength has followed industrious quadriceps exercise with 25 to 50 per cent increase in muscle power without increase in the volume of the thigh muscles.



Fig. 1—*a* Inexpensive spring scale used as dynamometer for testing quadriceps muscle. *b* 1. Spring scale. 2. Canvas bag for heel. 3. Canvas bag for heel. 4. Foot of variable weight as 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 901, 902, 903, 904, 905, 906, 907, 908, 909, 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, 924, 925, 926, 927, 928, 929, 930, 931, 932, 933, 934, 935, 936, 937, 938, 939, 940, 941, 942, 943, 944, 945, 946, 947, 948, 949, 950, 951, 952, 953, 954, 955, 956, 957, 958, 959, 960, 961, 962, 963, 964, 965, 966, 967, 968, 969, 970, 971, 972, 973, 974, 975, 976, 977, 978, 979, 980, 981, 982, 983, 984, 985, 986, 987, 988, 989, 990, 991, 992, 993, 994, 995, 996, 997, 998, 999, 1000.

Subsequently it was learned that an adaptation of the spring scale test described by Lovett^{14, 15} had been improvised. Recently Schmir¹⁶ and Mulek¹⁷ have employed more efficiently the same principle for assessing muscular strength. Jewes¹⁸ has determined the reliability of the spring scale method by means of a comparative study with the use of the electromyogram. He plotted the value of the two methods against each other and showed the close relationship between electromotive force and voluntary muscular contraction.

SELECTION AND PREPARATION OF PATIENTS FOR MENISCECTOMY

In general it may be stated that a careful estimate of the patient in the light of his occupation, his attitude, desire for work, physical and technical fitness have a direct bearing upon the usefulness of an operation. Largely

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The results of innumerable tests on forty patients during their reconditioning process indicated certain permissible inferences: (1) The maximum extensor strength of the thigh muscles ranges from 50 to 150 pounds. (2) The progress of muscle restoration can be accurately charted by repeated examinations. (3) The response to massage, physical therapy and exercise may be observed by detecting differences of muscle strength at interval examinations. (4) Excessive treatment or exercise may be first noticed by failure of increasing muscular power. During periods of inactivity little change and sometimes

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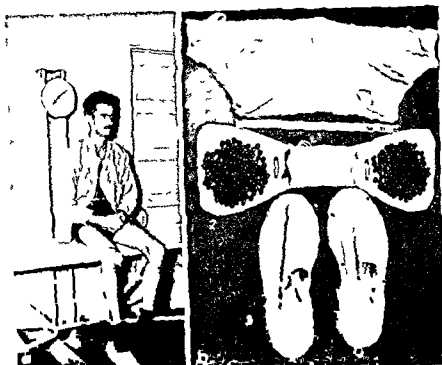


Fig 1-a Inextensible spring scale and dynamometer for testing quadriceps muscle strength. Short canvas bag being fastened to carry lead shot. Canvas bag for lead shot of variable weight as desired. Hip flaps upper rigid to hold dynamometer in spring scale test.

Subsequently it was learned that in adaptation of the spring scale test described by Lovett¹⁷ had been improved. Recently Schmier¹⁸ and Milch¹⁷ have employed more efficiently the same principle for assessing muscular strength. Fewer¹ has determined the reliability of the spring scale method by means of a comparative study with the use of the electromyogram. He plotted the value of the two methods against each other and showed the close relationship between electromotive force and voluntary muscular contraction.

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patients were selected for meniscectomy whose injury had been incurred in line of duty, and were not complicated by associated injuries such as osteochondritis dissecans, instability of the knee joint as the result of injury to the cruciate or collateral ligaments, arthritis chondromalacia of the patella, or severe traumatic synovitis.¹⁹ In addition to the usual preoperative care attention was given to the correction of hypotonia and atrophy of the quadriceps extensor muscles, in an effort to achieve some preoperative restoration of muscle function and to have the patient well trained for postoperative exercises. Each case was individualized and desirable nonweight bearing exercises were instituted.

Exercises—

- 1 Quadriceps extensor setting 1000 or more times a day
- 2 Patient supine in bed flexes the thigh to right angle and with weighted bag tied to the foot he slowly extends and flexes the leg
- 3 Patient prone in bed, foot in slipper which is attached through a pulley to a weighted bag actively flexes and extends the leg against resistance (Fig 2)



Fig 2—*a* Nonweight bearing exercises using weighted bag. *b* Weighted bag and pulley with slipper for leg and thigh exercises

Such nonweight bearing exercises when employed strenuously, were not associated with signs of joint irritation or subjective complaints. Progress was checked by measurements of the leg volume and the dynamometer tests.

MENISCLECTOMY

Two instruments were constructed (Fig 3) from sharp periosteal elevators for excision of the medial semilunar cartilage through an anterior incision into the joint. A modified Jones incision was used in the skin. The incision into the joint extended from a point the leg hanging at a right angle 15 cm. medial to the apical attachment of the ligamentum patellae obliquely downward and posterior dividing the fibrous fanlike membrane of the tibial collateral ligament²⁰ and ending at the parallel fibers on a level with the

coronary ligament The cartilage was usually freed anteriorly with ease. The liberation of the central portion of the cartilage was begun by the delineation of the superior and inferior capsular reflections which were separately divided along the periphery of the cartilage by the broad sharp dissector. By means of traction tension on the cartilage the areolar tissue binding the cartilage to the parallel portion of the tibial collateral ligament is made taut and easily separated with the dissector.

The oblique portion of the tibial collateral ligament is inseparably united to the joint capsule posteriorly and, accordingly, has been demonstrated^{21 22} to be joined to the meniscus. The knee is hyperflexed allowing the tibial collateral ligament to slide backward permitting easier access to the posterior

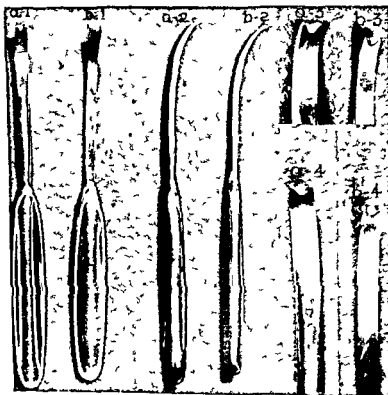


Fig 3 - The
actual size has
approximately
showing blunt

capsular attachment of the cartilage. The limited exposure could be further improved by adduction or abduction and rotation of the tibia on the femur, combined with digital pressure on the posterior joint capsule. The narrow dissector was employed to divide the superior and inferior capsular folds and the fibrous tissue uniting the capsule and the fibrocartilage. The freed cartilage is dislocated into the intercondylar notch and its posterior limb between the

lateral meniscus and the posterior cruciate ligament is divided under direct vision with the broad dissector. These instruments were a satisfactory addition to the usual devices employed to remove the semilunar cartilage.*

Forty one of forty nine patients operated upon for internal derangement of the knee joint were found to have injuries of the semilunar cartilage. The meniscus injuries were divided into three groups, longitudinal tears completely avulsed except for anterior and posterior attachments, and loose semilunar cartilages.

The largest group, thirteen of forty one patients sustained longitudinal tears of the semilunar cartilage of the bucket handle type. The average duration of disease was fourteen months. The symptoms and clinical findings were fairly constant and permitted an accurate diagnosis.

Completely avulsed cartilages attached anteriorly and posteriorly with the free portion lying in the intercondylar notch were found in eight cases. There were five patients with tears of the anterior portion of the cartilage, six with tears of the middle portion, and four posterior cartilage tears. These men had sustained their injuries twenty one months prior to an average of fifty two hospital days before surgery. In this analysis there were no characteristic complaints or findings on physical examination which would permit a diagnosis of the position of a partial tear of the cartilage. Brown² has reported the unreliability of McMurray's sign in tears of the posterior portion of the cartilage. In the absence of finding an accountable lesion in the anterior joint compartment the surgeon is committed to removal of the entire cartilage on the suspicion of a posterior tear.

In five cases examination of the meniscus at operation showed no fracture or dislocation of the cartilage but there was definite looseness beyond that considered normal. In addition the infrapatellar fat pad and adjacent synovium were hypertrophied; the cause of disability was undetermined. The history of these patients was not unlike that given for longitudinal tears of the cartilage. Two patients were found to have hypertrophy of the infrapatellar fat pad in the absence of any injury to the cruciate ligaments or abnormality of the semilunar cartilages. The history and physical examination were not pathognomonic of the condition found at operation. A recurrent cyst of the lateral cartilage which proved to have been incompletely removed and connected with the lateral cartilage was totally removed by means of two incisions into the joint capsule as employed by Cave and others.^{28, 29}

SUMMARY OF FOLLOW UP STUDY

A follow up questionnaire prompted by an earlier experience,²⁰ was sent through military channels to each man three months or more after leaving the hospital. Sixty five per cent replied. A subsequent study by Cave and others shows the thoroughness of such follow up studies when pursued with an interrupted continuity of effort. At the time this study was terminated† 10%

* Downing²⁴ have recently described semilunar cartilage knives
meniscus and the other
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men were returned to duty and 91 were separated from the service for disability of these 112 to whom questionnaires were sent had been discharged from the hospital four or more months. Seventy one replies were received. These indicate 60 per cent had continued military duty. Less than 60 per cent of the men separated from the service returned their questionnaires, however, 90 per cent of those who replied were performing work comparable to limited military service.

SUMMARY

More than 50 per cent of knee disabilities involving fracture and dislocation were found to be the result of internal derangement of the knee half required surgical treatment.

Menisectomy is an essential part of correcting internal derangement of the knee joint but in the absence of restoration of quadriceps muscle strength full weight bearing power of the leg will be delayed. Surgeons are generally careless as applied physiologists in combining surgical intervention and accepted means of restoring quadriceps muscle power in the treatment of knee joint disability. Postmenisectomy complaints in eighteen men were found to be due in more than one half to quadriceps atrophy and in two because of incomplete removal of the semilunar cartilage.

The spring scale muscle test is suitable for employment as an objective means of determining the progress of quadriceps muscle recovery after injury or arthrotomy of the knee joint. Failure to assess correctly quadriceps restoration may be the result of not employing such subjective measurements.

Undue delay of chondrectomy is undesirable as it allows development of quadriceps atrophy and often trauma to the articular surfaces of the femur.

An adequate follow up study on all patients treated in military hospitals and also those separated from the service is desirable in order to conserve the fighting strength of the army by ascertaining the effect of improved surgical and medical treatment.

LITERATURE

- 1 Boland E W and Carr W P. I. Rheumatic Rheumatism J. A. M. A. 123 805 809 1943
- 2 Stanek W F. Internal Derangement and Fractures Involving the Knee. Results of 150 Consecutive Arthrotomies Performed at Station Hospital of Bone & Joint Surg. 27 86 94 1945
- 3 Law W A. The Problems of Menisectomy in the Soldier J. Bone & Joint Surg. 28 496 500 1946
- 4 Grove E W. Hey. The Crucial Ligaments of the Knee Joint. Their Function, Rupture and Operative Treatment of Same. Brit J. Surg. 7 20 1913
- 5 American Medical Bulletin. Orthopedics. Dec. 1944
- 6 Watson Jones. Pagnall. The Williams & W.
- 7 Dixon W G. Internat.
- 8 West F E. Diagnosis North America 20
- 9 De Lorme T L. Restoration of Muscle Power by Heavy Resistance Exercises. J. Bone & Joint Surg. 27 645 667 1945
- 10 Thomas L. I. Review of 15 Cases of Arthrotomy of Knee Joints. Mil. Surgeon 98 70 24 1946
- 11 Peteron L T. The Quadriceps. Lectures on Reconstruction Surgery of the Extremities. A. A. O. S. Ann Arbor 1944. F. W. B. Brother. Inc., p. 31

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* "Dowling" have recently described a military cartilage knives and a "under the" in which the other cut by the the cartilage there remains only it.

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OLD UNITED AND UNUNITED FRACTURES OF THE PATELLA

JACK PASCHALL JR, M D,* RALPH K GHORMLEY, M D,† AND
MALCOLM B DOCKERTY, M D ‡ ROCHESTER MINN

THERE are very few references in the literature about the treatment of ununited fractures of the patella before the development of aseptic surgery.¹ Nonunions after patellar fractures were so common that they were accepted as good results. In 1878, Wyeth² reported an unsuccessful attempt to obtain bony union by injection of sheep marrow between the fragments. In 1881, 2 cases of ununited fracture of the patella were reported³ in which fixation of the fragments with silver wire was successful. Internal fixation gradually became accepted as the treatment of choice and the only disagreement among surgeons concerned the method to be used. Various surgeons reported their techniques and each one felt that his method was the best.⁴⁻⁶ In 1915, Phemister reported on the use of grafts of free fascia lata to connect the fragments. In 1927, Gallie and LeMesurier⁸ reported their method of repair, they used fascia or a segment of the Achilles tendon. In 1928, Albee⁹ recommended the use of an autogenous bone graft to hold the fragments and stimulate union.

The value of partial excision of the patella in treating ununited fractures was recognized shortly after Thomson¹⁰ reported its use for acute fractures in 1935. Since then Miltner¹¹ and Prince¹ have recommended partial excision for ununited fractures. Total excision of the patella for ununited fractures was reported as early as 1908 by Rogers.¹² He made two very bold statements for his time: (1) "The patella can be removed when ununited and perfect flexion and extension procured" and (2) "The patella should be removed when ununited or when repeated fracturing occurs." This method of treating ununited fractures did not gain favor until, as a result of Brooke's articles in 1937,^{14, 15} total excision became more widely used for acute fractures. In 1938 Tippet¹⁶ reported 3 cases in which ununited fractures were treated by total excision. In 1941 the same surgeon¹⁷ recommended total excision of the patella in a case of fracture of the patella complicated by patellofemoral arthritis. In 1942 Wass and Davies¹⁸ preferred total excision as the treatment for selected cases of patellofemoral arthritis following malunited fractures.¹⁹ In 1946 Horwitz and Lambert¹⁰ and MacAusland⁶ reported good results in cases of ununited and old fractures of the patella treated by total excision.

CLINICAL FINDINGS

Forty-two patients came to the Mayo Clinic between January, 1910, and January, 1946, because of old fractures of the patella. Thirty-eight of these patients had old ununited fractures and 4 had old united fractures. The majority of the patients had symptoms and signs of osteoarthritis in the involved patellofemoral joint. The static pain limited motion and muscular

Abstract of part of a thesis submitted by Dr. Paschall to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science.

- 12 Murray, C R Complicating Factors in Treatment of Injuries to the Menisci of the Knee Joint Am J Surg 55 262 273, 1942
- 13 Murray C R Treatment of Injuries to the Knee Joint, New England J Med 236 205 209 1947
- 14 Lovett R W, and Martin F G Certain Aspects of Infantile Paralysis With a Description of a Method of Muscle Testing J A M A 66 729 733, 1916
- 15 Lovett R W and Martin E G The Spring Balance Muscle Test, Am J Orthop Surg 14 415-424, 1916
- 16 Schmeer, A Research Work on a More Precise Method of Determining Muscle Strength in Poliomylitis Patients, New Muscle Tester J Bone & Joint Surg 27 317 326, 1945
- 17 Milch, H Measurement of Muscle Strength J Bone & Joint Surg 27 137 141 1945
- 18 Lewey, F H, Kuhn W G, Jr, and Juditsky J T A Standardized Method for Assessing the Strength of Hand and Foot Muscles Surg, Gynec & Obst 85 785 793 1947
- 19 Cave E F, Rowe C R and Yee L B K. Selection of Cases for Arthroscopy of the Knee in an Overcrowded General Hospital, J Bone & Joint Surg 27 683 697 1945
- 20 Burge R F A Sharp Dissector for Meniscectomy, SURGERY 16 956 958 1941
- 21 Brantigan O C and Voell A F The Tibial Collateral Ligament Its Functions Its Bursae and Its Relation to the Medial Meniscus, J Bone & Joint Surg 25 121 131 1943
- 22 Brantigan O C and Voell A F The Mechanics of the Ligaments and Menisci of the Knee Joint J Bone & Joint Surg 23 416 426 1941
- 23 Morrison C M A New Knee Cartilage Knife U S Nav M Bull 44 401 405 1943
- 24 Downing F Harold Semilunar Cartilage Knives J Bone & Joint Surg 30 241 244 1948 (Presented in a motion picture entitled 'Arthroscopy of the Knee' and demonstrated in a Scientific Exhibit at the Annual Meeting of the American Orthopaedic Association, Chicago Ill Jan 20-29 1947)
- 25 Brow J Manipulation of the Knee Joint
- 26 Cave J Bone & Joint Surg 27 683 697 1945
- 27 Brow J Bone & Joint Surg 27 683 697 1945
- 28 Charnley J Exposure of the Posterior Horn of the Medial Meniscus Lancet 2 171 1945
- 29 Fehlsman H Posterior Approach to the Knee Clin North America 36 157 181, 1947
- 30 Burge P F Incidence of Appendectomy in Four Unrelated Population Groups SURGERY 9 733 740 1941

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atrophy from which these patients suffered were typical of this type of arthritis. However roentgenograms in most instances did not show evidence of marked osteoarthritic changes. In the 4 cases of old united fractures, there were varying degrees of irregularity and hypertrophic changes in the patellofemoral joint. Longitudinal or chip fractures did not occur in this series which suggests that in fractures of this type the fragments almost always unite or at least when they do not unite disability does not result.

It was possible to treat 11 patients by conservative measures. In each case the fracture did not involve the articular surface and the symptoms and signs were minimal. Some form of operation was advised for the remaining 31 patients. Eight patients with ununited fractures and 1 patient with patellofemoral arthritis the result of an old united fracture were advised to have surgical treatment but refused. Eight patients with old ununited fractures were treated by internal fixation using beef bone screws catgut silk, or silver wire. Nine patients were treated by excision of the smaller fragment or fragments. Five patellectomies were done, 2 in cases of ununited fractures and 3 in cases of old united fractures with patellofemoral arthritis.

Thirty one of the 42 patients were traced for an average of 9.1 years. The results are shown in Table I. All of the patients treated by conservative measures obtained good results. Three of the 9 patients who refused to have surgical treatment were traced for an average of 9.0 years. In each case the condition was much worse and the symptoms were those of osteoarthritis. Seven of 8 patients treated by internal fixation were traced for an average of 12.3 years. In 4 cases the condition was not improved and in 2 there was some improvement, the result was excellent in only 1 case. Seven of the 9 patients treated by partial excision were traced for an average of 6.5 years. In 2 cases the results were excellent, in 4 cases the patients improved and 1 patient was no better after operation than before. The 3 patients who underwent patellectomy were traced for an average of only 1.6 years. In this short period 3 were improved and in the other 2 cases the 2 results were considered excellent. On the basis of the relatively few patients we see that partial excision of ununited fractures resulted in more improved patients than did the attempts at internal fixation. Total excision gave good results in both ununited fractures and symptomatic old united fractures.

TABLE I. RESULTS OF THE TREATMENT OF PATIENTS WITH OLD FRACTURES OF THE PATELLA

METHOD	PATIENTS	TRACED PATIENTS	AVERAGE FOLLOW UP (yr.)	RESULTS		
				EXCELLENT	IMPROVED	NOT IMPROVED
Resturance and physical therapy	11	5	3.2	4	5	
Burgers advised but patient refused	9	3	9.0			3
Internal fixation of fragments	8	7	12.3	1	-	4
Excision of smaller fragment or fragments	9	7	6.5	-	4	1
Total excision of patella	5	3	1.6	-	3	
Total	42	31	9.1	5	12	8

PATHOLOGIC ASPECTS

Specimens from 15 patients were available for gross and microscopic study. In 9 cases the patients had undergone partial excision for nonunion. In 5 cases the entire patellas were studied; in 2 there was nonunion and in 3 there was union with patellofemoral arthritis. Replacement of articular cartilage by fibrous tissue was the predominant finding on gross examination. The remaining cartilage showed evidence of degeneration such as furrowing and fraying. In some specimens erosion extended through to subchondral bone. The varying degrees of distortion of the normal gross outline and contour of the specimens probably contributed to the development of arthritis by upsetting the normal mechanics of the patellofemoral joint. Mild hypertrophic lipping of the borders of the articular surface was present in only 1 specimen.

Microscopically, in 13 of 15 specimens degeneration of the cartilage had taken place which was considered more marked than normal for the age of the patient. The work by Bennett and associates¹ on changes in the knee joint at various ages was used as a basis for the comparison. Whether or not we should label the changes in the patella 'osteoarthritis' (degenerative arthritis) or 'traumatic arthritis' is an interesting problem. The altered staining, clumping of cells, fissuring and fraying, irregularity of the bone cartilage zone and the replacement of degenerating cartilage by fibrous tissue are similar to the findings of Bennett and associates¹ and Allison and one of us (R. K. G.)²² in degenerative (osteo) arthritis. However in the articular cartilage of the patellas in our series the fibrous tissue replacement seemed to be the predominant finding. In some specimens fibrous tissue covered the surface of the hyaline cartilage and in some areas it filled in large defects in the cartilage. Moreover, the changes seemed to be imperfect attempts at repair rather than pure degeneration. There were many evidences of repair after trauma to the patellas. The displacement of cartilage into cancellous bone and replacement of the cartilage by bone is a very good example. The clefts filled with fibrous tissue are also examples. In his study of amputated specimens obtained after severe injury, Soto Hall²³ observed 'linear fractures' of articular cartilage and believed they might be factors in producing degeneration. Cox²⁴ suggested that trauma to the patella might cause fractures in the minute girders of cancellous subchondral bone and result in impairment of nutrition and degeneration.

There is experimental evidence to indicate that arthritis will develop after single traumatic insults. Key²⁵ produced what he called hypertrophic arthritis in the patellofemoral joints of rabbits by creating defects in the patellar surface of the femur. Bennett and Bauer²⁶ performed similar experiments in dogs and found that arthritis developed only when the patella was displaced from its bed. They said that cartilage cells have only feeble ability to proliferate. Experimentally created defects were healed by fibrous tissue which originated in the connective tissue of the bone marrow, in the marginal synovial membrane and apparently, in some instances from articular cartilage cells.

In the present study it was difficult to be certain where the fibrous tissue originated. The clefts and defects seemed to be filled with fibrous tissue arising from the marrow. At least, the fibrous tissue in the defects was continuous with the marrow. The surface fibrosis was connected with the surrounding synovia and with the fibrous tissue in the defects in the cartilage. Some fibrous tissue may have arisen from the site of the fracture during the process of healing. The fibrous tissue did not seem to arise from cartilage cells. It is impossible to say when the fibrous tissue was formed but it was present in 1 patella examined four months after the initial injury.



Fig. 1 (Case 1)—a An old fracture through the upper pole of the left patella with slight separation and tilting of the fragments. There is evidence of early union. b The same knee two years later showing consolidation of the fragments. Note the irregular articular surface of the patella.

REPORT OF CASES

CASE 1—A physician 29 years of age came to the clinic in May, 1945. His chief complaint was stiffness in the left knee. The stiffness had resulted from twelve months' immobilization required to obtain union after a compound fracture of the left femur. The knee had been manipulated under anesthesia two months before the patient came to the clinic. He had experienced pain for two weeks after the manipulation and had noticed rather marked effusion.

On examination moderate atrophy of the left quadriceps was noted. The knee could be fully extended but could be flexed only 40 degrees. Roentgenograms of the left knee revealed evidence of an old fracture through the upper pole of the left patella with early union (Fig. 1, a).

The patient continued his duties as house surgeon during the next two years and was reexamined in May, 1947. There had been moderate pain in the knee for about two months. The pain was aggravated by walking, climbing stairs and changes of weather. Results of

examination were essentially the same as before, there being only 40 degrees flexion. Roentgenograms revealed evidence of bony union at the site of the patellar fracture (Fig 1 b), but the articular surface of the patella had become quite irregular. Accordingly, arthrotomy was performed through a median parapatellar incision. The articular surface of the patella was found to be soft and shaggy. There was almost complete loss of about 10 cm. of cartilage from the medial part and near the lower pole of the patella. The cartilage on the medial femoral condyle adjacent to the patellar erosion was eroded. The patella was excised and the median parapatellar incision in the capsule was closed without suturing the quadriceps tendon to the patellar tendon. Quadriceps setting exercises were started on the second postoperative day. The patient played eighteen holes of golf four weeks after the operation. One year after patellectomy the patient had no pain except for that caused by changes of weather and that which occasionally followed climbing stairs. Full active extension and 100 degrees of flexion were present. Roentgenograms revealed no evidence of alar or osseous foci in the quadriceps tendon (Fig 2 a).

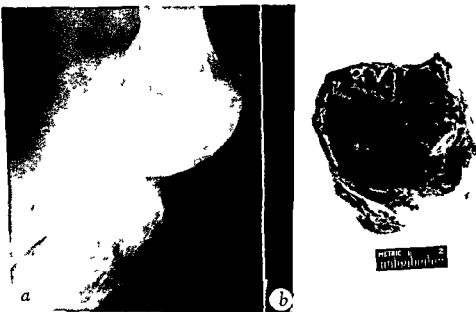


Fig 2 (Case 1) — a Same knee as in Fig 1 twelve months after patellectomy. There are no calcific or osseous foci in the quadriceps tendon. b Articular surface of the patella excised twenty six months after a transverse fracture. Note the shaggy strands of tissue attached to the rough cartilage. The normal contour of the ridge and facets has been distorted.

Pathologic Aspects—The general contour of the patella was slightly distorted and the articular cartilage was soft rough and irregular. Shaggy strands of tissue were attached to the surface particularly in the proximal half (Fig 2 b). Serial microscopic sections revealed a thin layer of vascular fibrous tissue that covered the hyaline cartilage in most areas. There was some fibrocartilage associated with the hyaline cartilage and there was moderate fibrillation of the matrix. The bone cartilage zone was quite irregular and new lamellae of bone were being formed about small blood vessels in the zone of calcified cartilage (Fig 3 a). The site of the fracture could be identified by a layer of hyaline cartilage that was displaced into the cancellous bone. This cartilage had been invaded by blood vessels and it was being replaced by bone (Fig 3 b).

Comment—This case serves as a good example of patellar fracture due to manipulation. The fracture was not discovered until malunion had occurred.

Two years later disabling patellofemoral arthritis was present. Patellectomy resulted in almost complete relief of pain and 60 degrees increase in motion.

The pathologic findings were those of traumatic arthritis.

CASE 2.—A professional football player 25 years of age first came to the clinic on May 27, 1932. He stated that three years and four months previously he had been thrown from his motorcycle and as he fell he struck the left knee against the concrete road. At the time he suffered moderate pain but was able to walk and ride the motorcycle again. There was considerable soreness and tenderness in the patellar region for six months after the accident but the patient did not consult a physician. On admission to the clinic his



b

Section through the middle part of it in distal face

chief complaints were weakness when crouching and springing forward and pain after prolonged exercise.

On examination he was found to have slight atrophy of the quadriceps. The upper border of the left patella was slightly tender and there was a palpable deformity in this region. There was a full range of active motion. Roentgenograms revealed an old ununited fracture of the proximal pole of the patella (Fig. 4).



Fig. 4



Fig. 5

Fig. 4 (Case 2).—The left knee shows evidence of an old ununited fracture of the proximal pole of the patella with some separation and tilting of the fragment. Note the difference in density of the two fragments and the sclerosis along the fractured surface of the distal fragment.

Fig. 5 (Case 1).—A section through the center of the medial facet of the excised fragment showing a wedge-shaped defect in the hyaline cartilage which has been filled in by fibrocartilage and fibrous tissue. Note the irregular bone cartilage zone ($\times 4$).

Arthrotomy was performed and the proximal fourth of the patella was found lying as a loose body in the quadriceps expansion. This fragment was excised and the tendinous structures were sutured back over the area. Active motion was started five weeks postoperatively and the patient returned to professional football four months after surgery. In answer to a letter of inquiry fifteen years later the patient said he had slight pain on severe exertion but motion and strength were unlimited.

Pathologic Aspects.—Grossly the articular surface of the excised fragment was uneven and furrowed. The surface of the fracture was covered with smooth fibrous tissue. Microscopically the articular cartilage was sutured and frayed and there was clumping of the cells. Fibrous tissue covered the surface in some areas and there were clefts and defects in the hyaline cartilage which were filled with fibrous tissue and fibrocartilage. The bone cartilage zone was quite irregular (Fig. 5). A layer of avascular fibrous tissue covered the fracture surface. There was some fibrocartilage mixed with the fibrous tissue and the surface cells were arranged in a compact layer three to four cells deep similar to synovial

tissue. It was interesting to find that the cancellous bone and marrow were normal in all respects because as was said, the fragment was found "lying as a loose body in the quadriceps expansion."

Comment—The fracture was produced by a direct blow and there was no rent in the quadriceps expansion, which allowed rather good function with little disability. Fixing the proximal fragment increased the strength of the knee and decreased the likelihood of disabling traumatic arthritis in subsequent years. Pathologically, there was evidence of early traumatic arthritis in the cartilage of the exposed fragment.



CASE 3—A businessman, 49 years of age, came to the clinic on Feb. 7, 1946. His complaints were stiffness and pain in the right knee. Six months previous to his admission he had been in a head-on collision, and had suffered fractures of both bones of the left forearm, a compound fracture of the right femur, and a fracture of the right kneecap. The fractures of the forearm were treated by open reduction and internal fixation. The fractured femur was treated by traction for six weeks, after which a long leg spica cast was used for two and one-half months. The only treatment for the fractured patella had been the immobilization used to obtain union of the fractured femur.

The patient walked with a cane and had a lump caused by the injured right knee. On examination there was marked atrophy of the quadriceps muscle of the right thigh. The patient could extend the leg fully but flexion was limited to 10 degrees. The patella was moderately enlarged and irregular in outline. Roentgenograms revealed evidence of an old comminuted fracture of the right patella with separation of the fragments (Fig. 6 a).

Arthrotomy was performed through a median parapatellar incision and the entire patella was excised. After this the knee could be passively flexed 30 degrees. The wound was closed without joining the patellar and quadriceps tendon. Active and passive motion was started on the eleventh postoperative day and continued daily for six weeks at the end of which time there was 30 degrees' active motion in the knee (150 to 155 degrees).

Six months later a letter from the referring physician revealed that motion remained the same. The patient did not return the questionnaire.

Pathologic Aspects—Examination of the patella revealed gross deformity of the articular surface (Fig 6 b). Microscopically, the articular surface was covered with fibrous tissue and some fibrocartilage. The hyaline cartilage which remained was covered with vascular fibrous tissue and contained clefts and defects filled with fibrous tissue. Union of the two major fragments was formed by fibrous tissue (Fig 7).



Fig 7 (C) and (D) — — — — —

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Comment—This is a good example of the result one should expect if a severely comminuted fracture of the patella is treated by immobilization. The fragments united by means of fibrous tissue and the articular surface became rough and irregular. Patellectomy increased motion 20 degrees and prevented the development of severe patellofemoral arthritis.

SUMMARY AND CONCLUSIONS

The clinical records of 42 patients with old and ununited fractures were studied. There were 35 ununited fractures and 4 symptomatic old united fractures. The results of the various methods of treatment were compared. Specimens from 15 cases of old or ununited fractures were studied grossly and microscopically. Three interesting cases which illustrate important clinical and pathologic findings were summarized and included.

Ununited fractures of the patella should be treated by total or partial excision. If the fracture is transverse it is often possible to excise the smaller fragment and leave the larger fragment to reattach to the quadriceps or patellar tendon. Old ununited comminuted fractures of the patella should be treated by patellectomy.

Disabling traumatic arthritis of the patellofemoral joint resulting from fractures of the patella should be treated by patellectomy whether the original fracture has united or not.

Varying degrees of traumatic arthritis of the patellofemoral joint probably develops after all patellar fractures. Certainly, some degree of traumatic arthritis develops in all cases of old ununited fracture of the patella.

In our study the majority of specimens revealed degeneration and replacement of hyaline cartilage by fibrous tissue. These findings appeared to be a combination of cartilage degeneration plus the results of injury and repair.

REFERENCES

- 1 Lister J. Remarks on the Treatment of Fractures of the Patella of Long Standing. *Lancet* 1 1049 1050 1908.
- 2 Wyeth J A. Fracture of the Patella. Injection of Animal Marrow Between the Fragments. *Med Rec* 13 567-568 1878.
- 3 Reports of Medical and Surgical Practice in the Hospitals and Asylums of Great Britain and Ireland (King's College Hospital). Two Cases of Ununited Fracture of the Patella Treated by Suturing the Fragments With Silver Wire. Also a Case of Ununited Fracture of Both Bones of the Forearm Treated in the Same Manner. *Brit M J* 1 919-920, 1891.
- 4 Bennett C A, and Bauer, Walter. Further Studies Concerning the Repair of Articular Cartilage in Dog Joints. *J Bone & Joint Surg* 17 141-150 1935.
- 5 Bruckner W M. The Patella, its Function and its Treatment for Old Fracture of the Patella.
- 6 Elmer W G. The Patella, its Function and its Treatment for Old Fracture of the Patella.
- 7 Phemister D B. Fascia Transplantation in the Treatment of Old Fractures of the Patella. *Ann. Surg* 62 746-748 1915.
- 8 Gallie W E, and LeMesurier A B. The Late Repair of Fractures of the Patella and of Rupture of the Ligamentum Patellae and Quadriceps Tenion. *J Bone & Joint Surg* 9 4 34, 1927.
- 9 Albee F H. Arthroplasty of the Knee. Fracture of Humerus With Non Union. Bone Graft for Scoliosis. Arthroplasty of Hip Following Arthroplasty. Un Union of Fracture of Neck of Femur. Bone Graft for Fracture of Patella. Non Union of Middle Third of Left Femur. *Internat Clin* 2 14-27 1904.
- 10 Thomson J E M. Communited Fractures of the Patella. Treatment of Cases Presenting One Large Fragment and Several Small Fragments. *J Bone & Joint Surg* 17 431-434 1935.
- 11 Miltner L J. Patella pty, Partial Excision of the Patella. *J Iowa M Soc* 29 50-503 1939.
- 12 Prince I D. Treatment of Fractures of the Patella by Partial Excision of Fragments. *Am J Surg* 53 23-30 1941.
- 13 Rogers C C. Removal of the Patella for Ununited Communited Fractures. *Illinois M J* 13 619-620 1908.
- 14 Brooke R. The Effect of Removal of the Patella for Simple Transverse Fractures on the Function of the Knee Joint. *Pro Roy Soc Med* 30 203-207 1937.
- 15 Brooke Ralph. The Treatment of Fractured Patella by Excision. a Study of Morphology and Function. *Brit J Surg* 24 7 54, 1937.
- 16 Tippet G O. Treatment of Fractures of the Patella by Excision. *Brit M J* 1 7 991-1000 1931.
- 17 M. Pres 206 16-160 1941.
- 18 n of the Patella for Fracture With Remark endon Following the Operation. *Cuv's Hosp*
- 19 atella tomy in the Military Service. a Report 423-441 1946.
- 20 atella for Fracture. Report of 14 Cases. *Am J Surg* 72 510-516 1946.
- 21 Bennett C A. Wayne Hans and Bauer Walter. Changes in the Knee Joint at Various Ages With Particular Reference to the Nature and Development of Degenerative Joint Disease. New York 1942. Commonwealth Fund 9 pp.
- 22 Allen N. Nathaniel and Ghormley R H. Diagnosis in Joint Disease. a Clinical and Pathological Study of Arthritis. New York 1941. William Wood & Company 196 pp.
- 23 Soto-Hall Ralph. Traumatic Degeneration of the Articular Cartilage of the Patella. *J Bone & Joint Surg* 27 4-6 431 1945.
- 24 Cox F J. Traumatic Osteochondritis of the Patella. *Quart J Med* 17 93-101 1916.
- 25 Key, J A. Experimental Arthritis. The Changes in Joints Produced by Creating Defects in the Articular Cartilage. *J Bone & Joint Surg* 13 72, 1931.
- 26 Bennett C A and Bauer Walter. A Study of the Repair of Articular Cartilage and the Reaction of Normal Joint of Adult Dogs to Surgically Created Defects of the Articular Cartilage. *Joint Micro and Patellar Displacement. Am J Path* 8 499-513 1932.

SOLITARY INTRATHORACIC NEUROFIBROMA

A REPORT OF TWO UNUSUAL CASES

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INTRODUCTION

DURING the past decade as mass roentgenography of the chest has become commonplace, increasing numbers of intrathoracic tumors are being detected and removed. Among them are certain solitary benign neurogenic tumors (neurofibromas) which characteristically are situated in relationship to the posterior mediastinum. Recently, we observed two cases in which a tumor of this type was present at a most unusual site. Accordingly, we are reporting our cases and reviewing the literature briefly in the hope that new interest will be aroused in the subject.

INCIDENCE

Intrathoracic neurogenic tumors once considered to be quite rare, are being reported with increasing frequency. Thus, while Epstein¹ in 1937 was able to collect only twenty-four cases from the entire literature, we estimate that approximately 180 cases have been recorded to date. If our own past experience constitutes a criterion, a far greater number of such tumors have been encountered than reported.

CLASSIFICATION

The histogenesis of neurogenic tumors remains a subject of controversy with the result that the terminology employed in the literature is not uniform. The vast majority of neurogenic intrathoracic tumors may be divided into two main groups. Group 1 includes those which arise from the nerve sheath, Group 2 consists of those which arise from the sympathetic nervous system.

Group 1—Tumors comprising Group 1 are, for the most part, benign in nature. They may arise from spinal, cranial or sympathetic nerves² and are composed almost always of both neural and connective tissue. There is considerable dispute concerning the precise element of the nerve sheath that gives rise to these tumors. Certain pathologists state that the endoneurium and perineurium are the primary source and that the lesions therefore are of mesodermal origin. These observers employ the descriptive terms neurofibroma and perineural fibroblastoma. Another group of pathologists believes that tumors of Group 1 arise from the Schwann cells of the neurilemma and that accordingly they are of ectodermal origin. These men employ the terms neurilemoma and Schwannoma. (Stout²⁵ recently stated that at present the consensus is that all benign nerve sheath tumors are of ectodermal origin.)

The literature is likely to confuse the reader further because certain authors do not differentiate between solitary benign nerve sheath tumors and tumors which constitute part of the widespread neurofibromatosis of von Recklinghausen's disease. Thus Cutler and Gross³ made no such distinction. On the other hand Stout² offered certain pathologic and clinical criteria for separating the aforementioned lesions into two distinct categories.

Group 2—Tumors comprising Group 2 arise from elements of the sympathetic nervous system. At times a single tumor may be composed of more than one type of nerve cell.²¹⁻²⁶ Also as pointed out by Dugan and Blides,⁸ the tumor may arise from the sheath of the sympathetic nerve giving rise to a neurofibroma or neurilemoma. Under certain circumstances, a tumor may be considered as of both sympathetic and nerve sheath origin.¹⁵⁻²¹ Thus, it becomes obvious that at times there may be some overlapping of cases in Groups 1 and 2. Fortunately, the precise origin of the tumors under discussion is of little practical significance.

Kent and associates,¹³ after analyzing a large series of cases reported that the *differentiated solitary, benign nerve sheath tumor (neurofibroma)* was the most common type of intrathoracic neurogenic tumor, with the ganglioneuroma next in frequency. Silvers and Adams⁷ are of the opinion that the neurofibroma is the most common benign mediastinal tumor. Our own analysis of the literature indicates that neurofibromas and ganglioneuromas have been reported in almost equal numbers.

INCIDENCE OF MALIGNANCY

Kent and co-workers¹³ reported that, in 105 cases of intrathoracic neurogenic tumor of all types 37 per cent were malignant. On the other hand, Maurer and associates¹⁷ stated that only approximately 10 per cent of such lesions were malignant. Regarding sympathetic nerve tumors malignancy depends upon the degree of cell maturity as is often the rule in other tumors arising from specialized tissues. Concerning nerve sheath tumors Stout states that lesions of the solitary neurilemoma (neurofibroma) group are not malignant. In cases of multiple neurofibromatosis however Hosoi¹⁴ estimated that malignant transformation occurred in approximately 13 per cent. Cutler and Gross³ believe that certain neurofibromas, which partake of the characteristics of both the neurofibroma and the neurogenic fibrosarcoma may become malignant. Such lesions grow more rapidly than benign lesions and often recur locally following extirpation. They do not metastasize, however. From all of the foregoing, it is apparent that the incidence of malignancy in neurogenic tumors is significant and has an important bearing upon therapy.

LOCATION

The vast majority of intrathoracic neurogenic tumors arise from neural elements which lie within or very close to the posterior mediastinum. Thus Kent and associates¹³ in a series of 123 cases found only four instances in which a solitary, benign neurofibroma was situated in the anterior mediastinum.

Occasionally, a neurofibroma may assume an hourglass or dumbbell shape, with part of the tumor lying within the posterior mediastinum and the remaining portion located in, or near the spinal canal. Under such circumstances, the lesion may be assumed to have arisen from nerve elements which are situated within the mediastinum, the vertebral canal, or the intervertebral foramina.¹² Solitary, benign intrathoracic neurofibromas are very rarely found in the lateral portions of the chest and in reviewing the literature, we were able to find reports of only two such cases.^{5, 9} Accordingly, we are reporting another case of this type the lesion being situated in the anterior axillary portion of the chest and arising from one of the intercostal nerves.

CASE REPORTS

CASE 1—R. F., a 39-year-old white woman was admitted to The Mount Sinai Hospital on Sept. 7, 1941 because of pain and the presence of a mass in the right chest of three months' duration. Three months previously during the course of a periodic health survey the mass was discovered on x-ray examination.

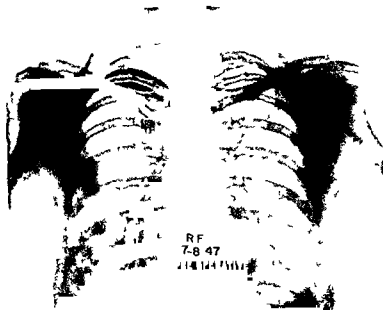


Fig. 1 (Case 1)—R. F. Posteroanterior film taken prior to operation. Note smooth ovoid lesion in axillary portion of right hemithorax.

Soon thereafter, the patient began to complain of mild intermittent discomfort in the substernal region and anterior portion of the right chest. This was associated with moderate tenderness on pressure in the latter area. There was no cough, dyspnea, or hemoptysis at any time during the illness. By the time the patient entered the hospital the pain had begun to diminish in intensity. At no time had any constitutional symptoms been present. The past history and family history were irrelevant.

X-ray examination in the posteroanterior position performed approximately one month after onset of symptoms disclosed an ovoid shadow in the axillary portion of the right hemithorax. The shadow extended from the level of the third to the fifth ribs (Fig. 1).

The shadow was well defined, had smooth contours and was of uniform density. When viewed in the left oblique position, it measured $2\frac{1}{2}$ by $1\frac{1}{2}$ inches in its vertical and transverse diameters respectively. The appearance of the lesion suggested that it was of extrapulmonary origin and probably originated in the thoracic parietes. The ribs revealed no abnormalities (Fig. 2).

On physical examination the patient appeared to be in excellent health. The only positive physical finding consisted of moderate tenderness anteriorly in the right axilla in the general region of the fourth and fifth ribs and intervening intercostal space. All laboratory findings were negative. The preoperative diagnosis was that of a benign tumor probably arising from the pleura.



Fig. 2 (Case 1).—R. F. 1st oblique film taken pre to operation. Note sharp delineation of tumor lying in anterior axillary region of right hemithorax. Tumor appears to originate in the thoracic parietes. The ribs appear normal.

On Sept. 4, 1947, thoracic exploration was performed by one of us (A. S. W. T.) under intratracheal halothane anesthesia. A short incision was made high in the right axilla anteriorly and the pleura entered through the third intercostal space. The lesion could not be palpated adequately through the existing small intercostal incision; accordingly, the third rib was divided at the anterior and posterior extremities of the skin incision. The doubly divided rib then was retracted cephalad and the intrathoracic abnormality visualized. It was noted at once that the tumor was situated outside of the parietal pleura and lay in close proximity to the fourth rib. Although the tumor extended into the thorax it was completely covered by and imbedded in the overlying parietal pleura. The latter could be stripped readily from the tumor. The mass was elastic and fleshy gray in color. Since it appeared to be intimately attached to the fourth rib, a further segment of the latter was removed together with the attached mass. The doubly divided third rib, which was still attached to the axonal intercostal muscle bundle, was retracted and immobilized with several sutures. A small 100,000 units was installed into the pleura and the lung reinflated by positive pressure. The thoracic parietes were closed in layers. Sulfate technique was employed throughout. The pleura was not drained.

The post-operative course was uneventful, the patient being discharged from the hospital on the seventh postoperative day with a well healed incision. At the time of discharge she was symptom free. A small collection of fluid which was present at the right base, resorbed spontaneously.

Pathologic report of the surgical specimen was as follows: The specimen consisted of a resected portion of rib measuring 8.5 cm in length with a roughly oval shaped cystic mass attached to its inner aspect. The mass measured 7 by 1 by 3 cm. It was completely encapsulated and could be dissected away from the rib, to which it was attached by fibrous tissue. The surface of the mass was smooth and in places was bluish in color. Pooled serous fluid could be aspirated from the interior. There was no destruction of the rib. The intercostal nerve could not be identified. The microscopic diagnosis was neurofibroma.

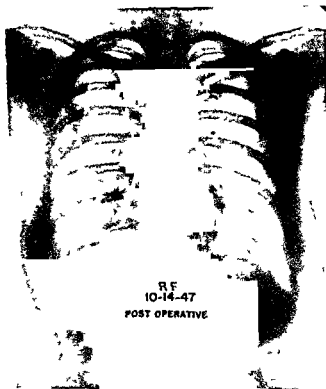


Fig 3 (Case 1).—P. A. Posteroanterior film taken five weeks after operation. Note that tumor has been removed with a segment of the fourth rib. The third rib has been divided and replaced.

X-ray examination of the chest performed five weeks after operation revealed the right hemithorax to be clear (Fig 3). During the two years since operation the patient has remained well and several x-ray films of the chest have failed to disclose any evidence of recurrence of the tumor.

Our second case, one of solitary benign intrapulmonary neurofibroma, was even more unusual than the first. Tumors such as the one about to be described apparently are excessively rare. Bartlett and Adams² stated that numerous cases of neurofibroma of the lung occurring in von Recklinghausen's disease have been reported. However a review of the references cited

The shadow was well defined had smooth contours and was of uniform density. When viewed in the left oblique position, it measured $2\frac{1}{4}$ by $1\frac{1}{4}$ inches in its vertical and transverse diameters respectively. The appearance of the lesion suggested that it was of extrapulmonary origin and probably originated in the thoracic parietes. The ribs revealed no abnormalities (Fig. 2).

On physical examination the patient appeared to be in excellent health. The only positive physical finding consisted of moderate tenderness anteriorly in the right axilla in the general region of the fourth and fifth ribs and intervening intercostal space. All laboratory findings were negative. The presumptive diagnosis was that of a benign tumor, probably arising from the pleura.



Fig. (Case 1) —R. F. Left oblique film taken just prior to operation. Note sharp delineation of tumor lying in anterior axillary region of right hemithorax. Tumor appears to originate in the thoracic parietes. The ribs appear normal.

On Sept. 8, 1947 thoracic exploration was performed by one of us (A. S. W. T.) under intratracheal cyclopropane oxygen anesthesia. A short incision was made high in the right axilla anteriorly and the pleura entered through the third intercostal space. The lesion could not be palpated adequately, through the existing small intercostal incision, accordingly the third rib was divided at its anterior and posterior extremities of the skin incision. The doubly divided rib then was retracted cephalad and the intrathoracic abnormality visualized. It was noted at once that the tumor was situated outside of the parietal pleura and lay in close proximity to the fourth rib. Although the tumor extended into the thorax it was completely covered by and indented the overlying parietal pleura. The latter could be stripped readily from the tumor. The mass was elastic and bluish gray in color. Since it appeared to be intimately attached to the fourth rib a four inch segment of the latter was removed together with the attached mass. The doubly divided third rib which was still attached to the second intercostal muscle bundle was replaced and immobilized with several sutures. Penicillin 100,000 units was instilled into the pleura and the lung reinflated by positive pressure. The thoracic parietes were closed in layers. Silk technique was employed throughout. The pleura was not drained.

The postoperative course was uneventful, the patient being discharged from the hospital on the seventh postoperative day with a well-healed incision. At the time of discharge, she was symptom free. A small collection of fluid which was present at the right base, resorbed spontaneously.

Pathologic report of the surgical specimen was as follows: The specimen consisted of a resected portion of rib measuring 9.5 cm in length with a roughly oval shaped cystic mass attached to its inner aspect. The mass measured 7 by 4 by 3 cm. It was completely encapsulated and could be dissected away from the rib, to which it was attached by fibrous tissue. The surface of the mass was smooth and in places was bluish in color. Blood stained fluid could be aspirated from the interior. There was no destruction of the rib. The intercostal nerve could not be identified. The microscopic diagnosis was "neurofibroma."

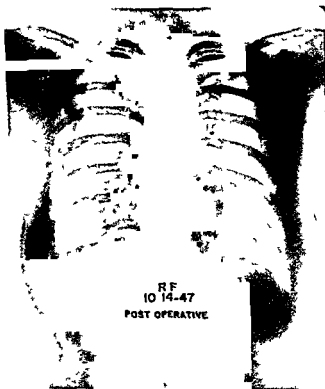


Fig. 3 (Case 1).—P. F. Posteroanterior film taken five weeks after operation. Note that tumor has been removed with a segment of the fourth rib. The third rib has been divided and replaced.

X-ray examination of the chest, performed five weeks after operation, revealed the right hemithorax to be clear (Fig. 3). During the two years since operation the patient has remained well and several x-ray films of the chest have failed to disclose any evidence of recurrence of the tumor.

Our second case, one of solitary benign intrapulmonary neurofibroma, was even more unusual than the first. Tumors such as the one about to be described apparently are excessively rare. Bartlett and Adams stated that numerous cases of neurofibroma of the lung occurring in von Recklinghausen's disease have been reported. However, a review of the references cited

revealed only one such case and in the afore mentioned case, sarcomatous involvement of the lungs was found. Blum²⁴ reported a case of von Recklinghausen's disease in which the x ray film disclosed an intrathoracic tumor which was assumed to lie within the lung. However, the patient was not subjected to operation and, accordingly, the diagnosis of intrapulmonary neurofibroma cannot be accepted without reservation.

Rubin and Aronson,²⁵ in 1940, described a case of neurofibromatosis limited to the lungs. In their case multiple nodules were found in, and on the surfaces of, both lungs. The pathologic report of these nodules was "neurofibroma or perineural fibroblastoma." There was no evidence of generalized von Recklinghausen's disease. Bartlett and Adams² in 1946, published a case in which a solitary neurogenic tumor was found attached to the left main bronchus. The mass lay, for the most part in the pleural space between the left upper and lower lobes. Pneumonectomy was performed, the tumor being reported a "neurinoma." Accordingly, the case which we are about to describe appears to be unique, in so far as it seems to be the only one in the literature in which a benign solitary neurogenic tumor has been reported to lie within the substance of the lung.

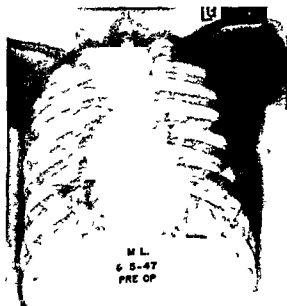


Fig. 4 (Case 2)—M. L. Posteroanterior film taken prior to operation. Note circumscribed shadow in right hilar region.

CASE 2—M. L. an 18 year-old white man was admitted to the Tumor Clinic of The Mount Sinai Hospital on June 3, 1947 a short time after a shadow had been discovered in the right side of the chest during the course of an Army pre induction examination. Aside from mild dyspnea on exertion he had no complaints referable to the chest. Neither cough, thoracic pain nor hemoptysis ever had been noted. He had lost approximately twenty five

pounds in weight during the eight months preceding admission without obvious reason. The family history was entirely irrelevant. The past history was negative except for cerebral concussion resulting from an automobile accident in April 1943. Since the accident, the patient had suffered intermittently from headache and dizziness.

Physical examination disclosed a somewhat thin young man who did not appear acutely ill. The weight was 108 pounds. The only positive physical finding was slight, generalized lymphadenopathy. Temperature, pulse and respirations were normal. All forms of laboratory examination were negative.



Fig. 3 (Case 2)—M. L. Lat. film taken prior to operation. Note smooth rounded tumor lying at junction of middle and posterior thirds of chest. (The typical position of a neurofibroma usually is further posteriorly.)

A posteroanterior roentgenogram of the chest made on June 5, 1947, revealed a circumscribed density measuring approximately 2 by 2 by 3 inches in the medial portion of the right hemithorax (hilar region) extending from the level of the sixth interpace to the eighth rib, posteriorly (Fig. 4). The roentgenogram aside from the presence of moderate pulmonary vascular congestion on the right was not remarkable. When viewed in the lateral position the tumor appeared to be smooth circumscribed and rounded. It was situated at the junction of the middle and posterior thirds of the chest and did not displace or encroach upon the barium-filled esophagus. It lay on a plane which, for the most

part, was anterior to the vertebral column (Fig 5). (It was of particular interest to note that the shadow did not occupy the paravertebral gutter, the most common site of neurogenic tumors which arise from the sympathetic nerve chain.)

In the tumor clinic, the diagnosis of atypical mediastinal lymphoma was seriously considered and a therapeutic test of radiation therefore advised. Accordingly a total of 1454 r was administered between July 8 and 31 1947. When this failed to influence the size and density of the mass the patient was referred to the surgical service of the senior author for further treatment.

When admitted to the hospital on Sept. 10 1947 the patient stated that he had been suffering sharp pain in the region of the right nipple and mid thoracic spine for three weeks. He added that the pain was increased by exercise and damp weather but that the dyspnea of which he originally complained no longer was present. He also had regained eight pounds in weight.

Physical examination revealed the same slight generalized lymphadenopathy which previously had been noted in the tumor clinic. A few coarse inspiratory rhonchi were noted posteriorly near the angle of the right scapula. Slight postirradiation pigmentation was present over the right breast. The remainder of the physical findings were noncontributory. All laboratory studies were normal.

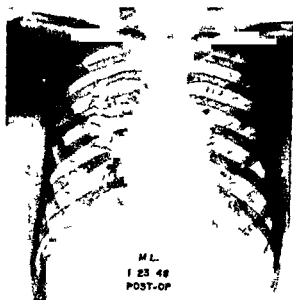


Fig 6 (Case 2).—M. L. Posteroanterior film taken approximately four months after operation. Note that tumor has been removed and is replaced by a fibrotic scar. The divided ends of the sixth rib have been replaced and welded.

On Oct. 1 1947 operation was performed by one of us (A. S. W. T.). A right-sided posterolateral thoracic incision was made through the sixth intercostal space after dividing the sixth rib close to the transverse process. When the pleura was opened a mass was noted in the apical portion of the lower lobe. The upper and lower lobes were united by a few stringlike adhesions which were divided in order to permit the lobes to be separated. After this had been accomplished and the interlobar (upper) surface of the lower lobe exposed a firm grayish white gentle swelling was noted projecting from the substance of the latter. The projection, which measured about $1\frac{1}{2}$ inches in diameter and $\frac{1}{2}$ inch in height comprised the summit of a rounded mass which lay within the substance of the apical portion of the lobe along its and on a plane anterior to, the vertebral column.

The pleura over the summit of the tumor was incised and the mass progressively dissected out of the pulmonary parenchyma. The lesion was found to be sharply circumscribed and well encapsulated. After it had been removed a few fine bronchial openings were noted in the tumor bed. Several small masses of fibrin formed into the pulmonary defect which then was closed with a series of interrupted mattress sutures of fine silk. After this had been completed the defect in the lung was pleuralized with another tier of sutures and 100,000 units of penicillin were instilled into the pleura. The residual air was removed from the pleura by catheter suction and the thoracic parietes were closed in layers without drainage.

The postoperative course was uneventful, the patient being discharged on the twelfth postoperative day with a well-healed wound.

The pathologic report of the surgical specimen was as follows: The operative specimen consisted of a lemon-sized firm mass. The lesion was well encapsulated and of yellowish gray color. Cut surface revealed a lumpy grayish yellow tissue in which there were many streaks. Interspersed between these areas, there were many small yellowish softer areas. In place, the latter were nodular and linear. Microscopic diagnosis was "neurofibroma."



Fig. 1 (Case 1)—M. L. roentgenogram film taken approximately one year after operation. Note the fibrous infiltration in extent of hilar scarring. No recurrence of tumor.

A film taken approximately four months after operation revealed the right hemithorax to be clear except for a few fibrotic streaks in the region formerly occupied by the tumor. The pulmonary vascular connection was still present (Fig. 6). The patient was gaining weight and had no complaints referable to the chest. He was last observed on Sept. 21, 1948. At that time he appeared in excellent general physical condition. His weight was 127 pounds and he was entirely symptom-free. An x-ray film taken on Sept. 19, 1948 (approximately one year after operation) revealed the chest to be entirely normal and the pre-existing right-sided pulmonary vascular connection to have disappeared (Fig. 7).

Comment—It is to be noted that in both of our cases the presence of an intrathoracic mass was detected accidentally during the course of routine x-ray

examination. It also appears that whatever subjective symptoms were present did not commence until after the patients became aware that a tumor was present. Although the diagnosis of a benign tumor was made in each instance because of the sharp circumscription of the lesion, the precise nature of the growth was not known, or even suspected, until operation was performed. Had the tumors been situated in the characteristic paravertebral position the correct diagnosis probably would have been made prior to operation. In Case 2 the presence of right-sided pulmonary vascular congestion as a result of pressure of a pulmonary tumor on the return circulation of the lung was of unusual interest.

Diagnosis.—The early diagnosis of benign intrathoracic neurogenic tumors is difficult because such lesions are likely to remain asymptomatic for a long period. Thus in our two cases, it is impossible to state the duration of the lesions which were found at operation. Symptoms of mediastinal compression, such as are common in cases of anterior mediastinal tumor are rare because the typical paravertebral site of the lesion permits the mass to expand freely into the pleural space and compress the lung rather than the structures within the mediastinum. Thus, mediastinal compression occurs only after the tumor has grown to an unusually large size.

It appears to be generally agreed that the most common subjective complaint is pain.^{9, 10, 11, 12, 13, 14} The latter usually is dull and aching in character and not uncommonly is of the "intercostal nerve" type. Pleural pain is stated to be rare.¹⁵ Overholt and Souder,¹⁶ and Harrington¹⁰ are of the opinion that pain becomes more marked when malignant degeneration occurs. Harrington also believes that the pain of malignant tumors is more severe at night than during the day. In the presence of an hourglass or dumbbell tumor neurological symptoms may be the presenting or predominant clinical feature as a result of spinal cord or root compression.

Physical examination, as a rule reveals no characteristic findings. Horner's syndrome or vocal cord paralysis may be present when the tumor is situated in the upper portion of the chest. Venous obstruction within the thorax occurs only when the tumor reaches unusually large size. The most important method of detecting these relatively asymptomatic tumors is by periodic roentgenography. Thus Blades⁷ reported that of 109 cases of mediastinal tumor encountered in the Army, 94 were discovered on routine x-ray examination of the chest.

In the film the tumor appears as a round or ovoid mass which lies in the extreme posterior part of the vertebral column (paravertebral gutter). (The rare exceptions to this location already have been discussed.) With tumors of the hourglass or dumbbell type pressure erosion of a vertebra may be noted in the region adjacent to the intervertebral foramen. Occasionally, areas of calcification may be present within the tumor.¹¹ When the lesion is lobulated or grows rapidly malignancy must be seriously considered.¹⁵

Regarding differential diagnosis in typical cases, the other less common tumors to be considered are fibromas, chondromas, osteomas, myxomas, and remnants of the foregut.¹ Precise determination of the type of neurogenic tumor is extremely difficult if not impossible, prior to operation.^{2, 3, 23} Nerve sheath tumors and nerve cell tumors have similar roentgenographic characteristics and growth patterns. The age of the patient may be of assistance in arriving at a diagnosis for, in general, malignant undifferentiated sympathetic nerve tumors tend to occur in infancy, ganglioneuromas in childhood, and nerve sheath tumors in adult life.²³

Therapy—All authors are in agreement that the only treatment of intrathoracic neurogenic tumors is surgical removal as soon as the lesion is discovered.^{1, 3, 11, 15, 16, 19, 21, 23} Even if no symptoms are present operative treatment is indicated because of the presence of malignancy or the danger of later development of malignancy.^{4, 23} Furthermore, the diagnosis of malignancy is sufficiently difficult and the incidence of malignancy sufficiently high to warrant operation without delay. Then again as the lesions enlarge they may produce pressure symptoms and become increasingly difficult to remove. Finally, the danger of operation is small in the hands of those with experience in thoracic surgery. Thus Blades reported that there were no deaths attributable to exploration in 114 cases of mediastinal tumor operated upon in the Army.

It is agreed that radiation is of little or no value in the treatment of benign neurogenic tumors. Even malignant growths of such origin are little affected and knowledge of this fact has led to the use of radiation therapy as a diagnostic test in cases in which a lymphoma is suspected. A dose of 1000-1500 r delivered over the center of the mass should produce regression of a lymphoma within one month. If such change does not occur the diagnosis of lymphoma should be discarded immediately and operation performed, as in our case of intrapulmonary neurogenic tumor (Case 2).

SUMMARY

Two cases of solitary benign intrathoracic nerve sheath tumor (neurofibroma) in which the lesions were atypically situated are reported.

In the first case the tumor was situated in the right anterior axilla and was derived from the fourth intercostal nerve. In the second instance the lesion was found imbedded in the apical portion of the right lower lobe. Both cases constitute rarities in the literature.

In each instance, the lesion was discovered accidentally during routine roentgenographic examination of the chest.

The general subject of benign intrathoracic neurogenic tumors including diagnosis and treatment is reviewed.

REFERENCES

- 1 Alexander J. Circumscribed Intrathoracic Neoplasms. *J. A. M. A.* 119: 390, 1942.
- 2 Bartlett J. I. and Adams W. E. Solitary Primary Neurogenic Tumor of the Lung. *J. Thoracic Surg.* 15: 241, 1946.
- 3 Blades B. Mediastinal Tumors. *Ann. Surg.* 123: 749, 1946.
- 4 Clagett O. T. and Haumann O. F. Huge Intrathoracic Fibroma. *J. Thoracic Surg.* 13: 6, 1944.

examination. It also appears that whatever subjective symptoms were present did not commence until after the patients became aware that a tumor was present. Although the diagnosis of a benign tumor was made in each instance because of the sharp circumscription of the lesion, the precise nature of the growth was not known or even suspected until operation was performed. Had the tumors been situated in the characteristic paravertebral position the correct diagnosis probably would have been made prior to operation. In Case 2, the presence of right-sided pulmonary vascular congestion, as a result of pressure of a pulmonary tumor on the return circulation of the lung was of unusual interest.

Diagnosis—The early diagnosis of benign intrathoracic neurogenic tumors is difficult because such lesions are likely to remain asymptomatic for a long period. Thus in our two cases, it is impossible to state the duration of the lesions which were found at operation. Symptoms of mediastinal compression such as are common in cases of anterior mediastinal tumor, are rare because the typical paravertebral site of the lesion permits the mass to expand freely into the pleural space and compress the lung rather than the structures within the mediastinum. Thus mediastinal compression occurs only after the tumor has grown to an unusually large size.

It appears to be generally agreed that the most common subjective complaint is pain.^{8, 9, 10, 11, 12} The latter usually is dull and aching in character, and not uncommonly is of the 'intercostal nerve' type. Pleural pain is stated to be rare.¹¹ Overholt and Souders,¹³ and Harrington¹⁰ are of the opinion that pain becomes more marked when malignant degeneration occurs. Harrington also believes that the pain of malignant tumors is more severe at night than during the day. In the presence of an hourglass or dumbbell tumor, neurological symptoms may be the presenting or predominant clinical feature as a result of spinal cord or root compression.

Physical examination, as a rule, reveals no characteristic findings. Horner's syndrome or vocal cord paralysis may be present when the tumor is situated in the upper portion of the chest. Venous obstruction within the thorax occurs only when the tumor reaches unusually large size. The most important method of detecting these relatively asymptomatic tumors is by periodic roentgenography. Thus, Blades³ reported that of 109 cases of mediastinal tumor encountered in the Army, 94 were discovered on routine x-ray examination of the chest.

In the film, the typical benign intrathoracic neurogenic tumor appears as a round or ovoid sharply circumscribed uniform density which lies in the extreme posterior portion of the hemithorax close to the vertebral column (paravertebral gutter). (The rare exceptions to this location already have been discussed.) With tumors of the hourglass or dumbbell type pressure erosion of a vertebra may be noted in the region adjacent to the intervertebral foramen. Occasionally, areas of calcification may be present within the tumor.¹¹ When the lesion is lobulated or grows rapidly, malignancy must be seriously considered.¹²

WOUND HEALING AND HEPARIN, USING HEPARIN DEPOSITS

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IT IS generally assumed that the first union of approximated wound surfaces is by fibrin from plasma or blood. It is believed that fibrin forms a scaffold for the formation of uniting, fibroblastic growth, and that, therefore the function of the fibrin clot is important for healing.¹ The next step consists in the bridging of the gap between the wound surfaces by histiocytes and capillaries. The fibrin clot between the surfaces of the wounds probably disappears either by lysis or by macrophages. Administration of anticoagulants would seem therefore to be able to prohibit the primary union of wounds, and the absence of a network of fibrin between wound surfaces might delay secondary healing. Yet experimental results on the effect of anticoagulants on the healing process are controversial. Murray and Best² found no inhibition of healing of incisions in blood vessels by heparin. Lehman and Boys³ reported on the prevention of peritoneal adhesions with heparin. In our own work, interrupted by World War II we did not observe inhibition of healing by heparin. Our results were confirmed and reported by others.⁴ Alrich and Lehman¹ found that tensile strength of wounds in heparinized rabbits was less than in nonheparinized control animals. They remarked, however that twice as many heparinized than nonheparinized rabbits died and that this mortality may have introduced a selective factor into their experiments. Heparin has been reported to depress growth of tumor cells and of embryonic cells in tissue culture.^{5, 6}

Our interest in possible effects of anticoagulants on wound healing was aroused by an observation in 1941 on a heparinized male patient with complete disruption of an inguinal herniorrhaphy wound three days after operation. The edges of the wound showed no indication of healing. Blood clotting time was between 15 and 20 minutes when disruption of the wound occurred. Although similar incidents have been observed on nonheparinized patients the seriousness of the problem impressed us sufficiently to undertake a study on the rat and the dog. This was interrupted by war service of one of us (R M B) and was not completed until now. Since the effect of anticoagulants on healing is still controversial and since our experiments have not been reported by ourselves nor in any detail⁴ we are presenting them here. Furthermore we have applied a technique of heparinizing animals with a heparin benzidine salt depot, which simplified experiments so much that our experience may be useful to others.

Experiments on Depot Heparin — A suspension of protamine heparin* complex was found either ineffective or of unreliable action confirming the work

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- 5 Cutler F C and Gross R F Neurofibroma and Neurosarcoma of Peripheral Nerves Arch Surg 33 733, 19 6
- 6 Dugan D J, and Blade, B Resection of the Left Vagus Nerve for Multiple Intrathoracic Neurofibromas J A M A 123 409 1943
- 7 Epstein N Neurofibromatosis With Intrathoracic Neurofibroma New England J Med 216 551 1937
- 8 Gnanades G J Cervicothoracic Neurofibromatosis J Mt Sinai Hosp 10 414, 1943
- 9 Harrington R W Surgical Treatment of Intrathoracic Tumors Arch Surg 19 18, 9 1929
- 10 Harrington R W Surgical Treatment in 14 Cases of Mediastinal or Intrathoracic Perineurial Fibrosarcoma J Thoracic Surg 3 340 1944
- 11 Harrington R W, Borsey J M and Strohl P I Intrathoracic Tumor (Fibrosarcoma) S Clin North America 15 1123, 1941
- 12 Heuer, G J In Nelson's New Look at Leaf Surgery Vol 4 p 471 1943
- 13 Hollingsworth R Intrathoracic Tumors of Sympathetic Nervous System Surg Gynec. & Obst 82 68, 1946
- 14 Hewes K Multiple Neurofibromatosis With Special Reference to Malignant Transformation Arch Surg 22 218 1931
- 15 Kent F M, Blades R, Vakk A R and Graham F A Intrathoracic Neurogenic Tumors J Thoracic Surg 13 116 1944
- 16 Lavelle H and Irentice H Intrathoracic Neurofibroma Arch Surg 40 93 1940
- 17 Maurer A, Sauvage R and Mathey J Intrathoracic Tumors of Nervous Origin Mem Acad de chir 71 19 1915
- 18 Overholt R H and Scullers C R Benign Intrathoracic Tumors S Clin North America 17 969 1927
- 19 Poppel I D Neurofibroma of the Inferior Mediastinum SURGERY 2 819 1941
- 20 Rubin F H and Aronson, W Primary Neurofibroma of the Lung Am Rev Tuberc 41 801 1940
- 21 Schaffner, A D, Smith I I and Taylor, H F Primary Neurogenic Tumor of the Mediastinum J Thoracic Surg 12 247 1944
- 22 Silvers J and Adams R Benign Mediastinal Tumor, S Clin North America 27 596 1944
- 23 Skinner G F, Branch A and Allen J Ganglioneuroma of the Mediastinum Canad M A J 49 397 1943
- 24 Stout A I Human Cancer Histology 19 Lea & Febiger p. 76
- 25 Stout A I Neurofibroma and Neuroileoma J Capton Int'l Med 5 1 1946
- 26 Wall H and Robinson D Neuroblastoma of the Mediastinum With Pleomorphic Blastomatous Elements Arch Path 35 171 1943

mercury manometer, and a pressure bulb. The stomach was placed under water and held down manually. Then air was pumped slowly into the stomach, until the suture line gave and air bubbles escaped. The height of the mercury column at that moment was noted and the breaking point was registered in millimeters of mercury. After a number of control experiments on nonheparinized rats, the fifth postoperative day was chosen as most favorable for our test. At this time approximately 50 per cent healing seemed to have occurred. In the dog the sixth postoperative day was used for the pressure test.

In the experiments on dogs, in addition to the test on the stomach the tensile strength of the abdominal wound was measured. The skin sutures were removed and a glass cannula was tied securely in a small incision through the abdominal wall in the flank. The same method as used for the stomach of the rat was employed and the pressure was noted at which separation of the tissues of the wound occurred. In most tests the skin wound opened first and the fascial and peritoneal wounds second.

In view of the high cost of heparin and in order also to investigate the effect of Dicumarol on wound strength a number of experiments were carried out with that substance. Dicumarol* was administered by mouth in daily doses of 25 to 5 mg. per kilogram of body weight. Clotting and prothrombin times were checked daily. Both were elevated from 50 to several 100 per cent throughout the experimental period.

RESULTS

Table I shows that the breaking point of the gastrostomy wound in control rats is most uniform 5 days after operation and that from that point on the values are more scattered. Five days after operation the average value of the breaking points of the gastrostomy wounds was the same in heparinized as in nonheparinized animals (Table II). A scattergram showed no significant difference between the distribution of the values of both groups. Clotting times in Table II were taken at the 5 day period in the nonheparinized control rats; clotting times were almost uniform at 3 minutes (Table I).

In the dog experiments the 6 day period after gastrostomy was chosen as end point. One animal (Dog 9) received injections of heparin only to keep his clotting time elevated throughout the 6 day postoperative period. The control clotting time was 3 minutes; during heparinization clotting times were determined twice daily. They varied between 7½ and 35 minutes and at one determination only they had dropped to 2 minutes. In the morning and at noon ½ cc. of heparin per kilogram was administered subcutaneously and at night 1 cc. per kilogram subcutaneously. In the case of Dogs 10 and 11 the heparin benzidine complex was injected as indicated in Table IV.

It is seen from Table III that the strength of the gastric and abdominal wounds in the control animals (Dogs 1 to 8) and in the heparinized animals (Dogs 9 to 11) was within the same range. In Dog 11 the resistance of the gastric wound was at the lowest level of the controls. However this animal had pneumonia which may have affected healing.

* kindly supplied by Dr. R. K. Richards of the Abbott Laboratories, North Chicago, Ill.

of Charney and Olson⁸ and of Jaques and co-workers.⁹ An attempt to form a procaine heparin compound was unsuccessful. The benzidine heparin salt described by Jaques and associates⁹ was found to provide adequate heparinization in rats and dogs. The compound is used in the form of a fine precipitate which resembles that of protamine insulin. Aqueous benzidine HCl (a 5 per cent solution was used) precipitates heparin quantitatively. The precipitate is removed from the supernatant by centrifugation, washed with 0.5 per cent benzidine solution, re-centrifuged, washed and finally suspended in isotonic saline solution to make up a volume equal to that of the heparin solution used originally. Thus 1 cc of the suspension contained 10 mg. (1000 units) of heparin. The suspension was injected subcutaneously in amounts of 53 mg. (0.6 cc per kilogram) of heparin per kilogram of body weight in the dog and 5 mg. (0.5 cc) in the rat (average weight 300 Gm.). The injections did not produce sloughs or apparent pain in the animals. The heparin is liberated slowly from the compound, maintaining an elevated clotting time for up to 24 hours. For measuring clotting time the method of Lee and White was employed.

Method for Measuring Wound Strength—Adult albino rats and mongrel dogs of both sexes were used. The animals were in a normal state of nutrition and had normal total plasma protein and blood hemoglobin levels. Under sodium pentobarbital anesthesia in a sterile operation the abdomen was opened in the midline. The stomach was brought into the incision and a clean vertical cut was made through the entire thickness of the anterior wall of the prosthomaeh in the rat and the fundus in the dog. The length of the incision was 1 cm. in the rat and 4 cm. in the dog. The incision was closed in the rat by six interrupted stitches through all layers of the stomach using 0000 plain catgut. The abdomen was closed in two layers and the skin wound was covered with iodine collodion. In the dog the stomach was closed by eight interrupted stitches and by a Lambert serosal suture and the abdomen was closed in three layers. Catgut was used for all sutures except those of the skin where cotton was employed. The heparin benzidine complex suspension was injected immediately after operation. The animals received one subcutaneous injection in the morning and another one at night. Repeated tests of blood clotting time were performed in the dogs in order to insure the presence of elevated clotting times throughout the duration of the experiment. In the rat repeated withdrawal of blood was detrimental and clotting times were determined at the termination of experiment only. However, intermediary clotting times taken on twelve control rats showed the presence of satisfactory 24 hours heparinization. The animals recovered from the operation within 2 to 3 hours and were put back on the stock diets. After a number of days specified in the tables they were sacrificed painlessly.

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TABLE III HEALING OF WOUNDS IN CONTROL DOGS AND IN DOGS WITH HEPARIN BENZYLATE OR DICUMAROL

DOG NO.	SEX	WEIGHT (IN KG.)	DAYS AFTER CASTING TOMB	TREATMENT	HEALING POINT IN MM. HG.			REMARKS
					SKIN	PERITONEUM AND FASCIA	STOMACH	
1	F	3.0	6	None			Nil	
2	M	9.0	6	None			Nil	
3	F	0.4	6	None	140	100	80	Lower end of skin incision infected
4	F	10.1	6	None		200	70	Skin wound slight infection
5	M	6.2	6	None		+ 00	110	
6	F	3.0	6	None		165	40	
7	M	8.0	6	None		280	70	Skin wound incomplete healing
8	M	4.2	6	None		150	70	
9	M	7.3	6	Heparin only		140	110	Skin wound infected
10	F	6.0	6	Heparin benzylate		210	50	neumonia
11	F	8.0	6	Heparin benzylate	---	+	50	1 cm. of abdominal wound opened
12	M	5.4	3 (died)	Dicumarol				yellow liver, pneumonia
13		3.8	1	Dicumarol			40	Hemorrhage from abdominal wound subcutaneous hemorrhage, bronchopneumonia liver pale
14		4.6	3 (died)	Dicumarol	260	10	60	Liver yellow
15		1.6	2 (died)	Dicumarol			70	subcutaneous hematoma, liver yellow, bronchopneumonia

TABLE I HEALING OF GASTROSTOMY WOUNDS IN NONHEPARINIZED RATS

RAT NO	NUMBER OF DAYS	BREAKING POINT (IN MM HG)
1	5	42
2	5	50
3	5	68
4	5	76
5	5	76
6	5	78
7	5	78
8	5	88
9	5	88
10	5	88
11	5	94
12	5	112
13	6	60
14	6.5	88
15	6.5	134
16	6.5	148
17	6.5	140
18	6.5	200+
19	7	100
20	8	110
21	8	110
22	8	14
23	8	140
24	9	200+
25	9	200+
26	8	200+
27	13	178

TABLE II HEALING OF GASTROSTOMY WOUNDS IN HEPARINIZED AND NONHEPARINIZED RATS FIVE DAYS AFTER OPERATION

EXPERIMENT NO	HEPARINIZED		NONHEPARINIZED
	CLOTTING TIME (IN MIN)	BREAKING POINT (IN MM HG)	BREAKING POINT (IN MM HG)
1	12	10	4
2	15	50	50
3	15	68	68
4	17	68	76
5	21	76	76
6	17	84	78
7	18	88	78
8	20	94	88
9	18	98	88
10	19	104	88
11	20	152	91
Average			112
			78

The dogs that had received Dicumarol died or had to be sacrificed before the end of the 6 day period. All of them had serious pathologic findings as detailed in Table III, such as pneumonia, fatty infiltration of the liver and hematomas. In a number of them total plasma protein and albumin levels decreased considerably during the postoperative period. Yet the tensile strength of the stomach wounds between 40 and 70 mm of Hg 2 to 4 days postoperatively can be considered to be quite sufficient to withstand any intragastric pressure.⁴¹

However we have no controls without Dicumarol we were discouraged to procure these, in view of the complications encountered in every Dicumarinized animal not only in the present experiments but also in another, larger series of dogs in which the effect of Dicumarol of liver function was tested. In the latter work (unpublished) we had evidence that Dicumarol decreased liver function (phenolsulfalein excretion) in the absence of loss of blood by hemorrhage or hematoma. Also the effects of Dicumarol are not as easily controlled as those of heparin. Secondary factors like fever may increase its anticoagulant effect very considerably.¹⁶ Dicumarol appears to have more generalized effects than has heparin. It has been reported to affect capillary permeability and we have seen fatty infiltration of the liver in animals in which autopsies had revealed absence of hemorrhage. In all animals under Dicumarol regime the plasma protein levels dropped the albumin always more than the globulin. Since these dogs lost appetite and weight the lower plasma protein levels may have been due to this. Yet we have the impression from two animals who did not bleed nor lose appetite or weight during Dicumarinization but whose plasma albumins dropped that Dicumarol affects albumin production in the liver directly.

SUMMARY AND CONCLUSIONS

Heparinization of rats and dogs following laparotomy and gastrostomy did not affect the strength of the healing wounds. The effects of Dicumarol on wound healing in the dog are doubtful and the use of this drug appears to warrant more caution than the use of heparin.

The heparin benzidine complex has been found practical for prolonged heparinization of rats and dogs.

REFERENCES

1. Alrich F M and Lehman E I. *Surg Gynec & Obst* 87: 26 1948
2. Murray G D W and Be t C H. *Ann Surg* 108: 11 1938
3. Lehman E P and B y F. *Ann. Surg* 11: 427 1940
4. Laufman H J and Heller I E. *Surg Gynec & Obst* 76: 655 1942
5. Cerner A. *J Lab & Clin Med* 16: 309 1931
6. Zakrzewski A. *Klin Wchnschr* 11: 11* 1933
7. Fisher A. *Protoplasma* 26: 244 1934
8. Chargaff F and Olson K B. *J Biol Chem* 122: 153 1937
9. Jaque I B, Charles A F and Be t C H. *Acta med Scandinav (Suppl)* 90: 190, 1938
10. Bartlett M K, Jones C M and Ryan, A F. *New England J Med* 226: 419 1942
11. Alvarez W C. *An Introduction to Gastroenterology*, ed 4. New York 1948. Paul B Hoeber, Inc.
12. Figgion R H. *Proc Soc Exper Biol Med* 50: 54 1942
13. Jaque I B. *J Biol Chem* 133: 445 1940
14. Foote N C. *Pathology in Surgery*. Philadelphia 1945. J B Lippincott Company p 24
15. Gehrmann C H. *J Urol* 31: 154 1934
16. Piehler P K. *Science* 97: 313 1947

TABLE IV THE EFFECT OF HEPARIN BENZIDINE SALT ON BLOOD CLOTTING
(IN MALE DOG WEIGHING 13 KILOGRAMS)

DATE	TIME	INJECTION	CLOTTING TIME (IN MIN.)
11/ 5/1947	9 30	Heparin benzidine subcutaneous, 50 c.c. per kg.	6
	9 40		
	10 10		8
	10 40		12
	12 00		13
P M	5 00	Heparin benzidine subcutaneous 50 c.c. per kg.	+20
	9 00		17
	11 10		
11/ 6/1947			
A M	9 10		11
	11 30		14
P M	3 10		10
	4 30		8

DISCUSSION

It appears from our results that, in the rat heparinization during the healing period of a gastric incision does not diminish the strength of the wound as determined by our method. Likewise, in the dog there was no evidence in three animals receiving heavy doses of heparin that healing of abdominal wounds and of the gastric incision were impaired.

The lack of diminution of wound strength in heparinized animals appears *contradictory to the known facts about inhibition of fibrin formation by heparin*. However while the mechanism of blood clotting has been and is being studied extensively we know little about the mechanism of fibrin formation on surfaces of wounds. Heparin may be destroyed or inactivated in wounds by coagulase from bacteria¹² by proteases or heparinase¹³ or by substances which accelerate clotting (like globulin), such substances may be present in wounds in greater concentration than in the blood and thus fibrin formation may be normal. On the other hand the living of a fibrin structure may not be essential in primary healing of wounds. Foote¹⁴ has described the process of wound healing to consist in the multiplication of fibroblasts and a concomitant production of intercellular fibrils which are distinct from fibrin as proved by special stains. These fibrils form a network which becomes denser as collagen forms ending in the production of scar tissue.

The use of heparin benzidine complex proposed by Jaques⁸ has been successful in our hands. One to two subcutaneous injections per 24 hours seem to be sufficient to prolong clotting of blood in the rat and in the dog above 50 per cent (Table IV). We do not propose the use of the heparin benzidine salt in man because benzidine (bi aniline) is suspected to be carcinogenic although apparently only when it acts over prolonged periods of time.¹⁵

In the case of dogs receiving Dicumarol the evidence that the healing process is not affected is not as clear as in the case of heparin. Three of the four dogs in this series died 2 to 3 days after the operation and Dicumarol treatment. The fourth animal had to be sacrificed on the fourth day. In view of the short period of time after operation the wounds showed considerable strength approaching the lower levels of the dogs in the heparin series (Dogs 6 and 7).

However we have no controls without Dicumarol, we were discouraged to procure these, in view of the complications encountered in every Dicumarinized animal not only in the present experiments but also in another larger series of dogs in which the effect of Dicumarol of liver function was tested. In the latter work (unpublished) we had evidence that Dicumarol decreased liver function (phenolsulfalein excretion) in the absence of loss of blood by hemorrhage or hematoma. Also the effects of Dicumarol are not as easily controlled as those of heparin. Secondary factors like fever may increase its anticoagulant effect very considerably.¹⁶ Dicumarol appears to have more generalized effects than has heparin. It has been reported to affect capillary permeability, and we have seen fatty infiltration of the liver in animals in which autopsies had revealed absence of hemorrhage. In all animals under Dicumarol regime the plasma protein levels dropped the albumin always more than the globulin. Since these dogs lost appetite and weight the lower plasma protein levels may have been due to this. Yet we have the impression from two animals who did not bleed nor lose appetite or weight during Dicumarinization but whose plasma albumins dropped that Dicumarol affects albumin production in the liver directly.

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Heparinization of rats and dogs following laparotomy and gastrostomy did not affect the strength of the healing wounds. The effects of Dicumarol on wound healing in the dog are doubtful and the use of this drug appears to warrant more caution than the use of heparin.

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REFERENCES

1. Ulrich E M and Lehman F I. *Surg Gynec & Obst* 87 26 1948
2. Murray G D W and Bick C H. *Ann Surg* 108 16 1938
3. Lehman F I and Poy F. *Ann Surg* 11 4 1940
4. Laufman H J and Heller P E. *Surg Gynec & Obst* 76 60 1943
5. Coerner A. *J Lab & Clin Med* 16 20 1933
6. Zakrzewski A. *Klin Wchnschr* 11 113 1933
7. Fisher A. *Protoplasma* 26 344 1931
8. Chargaff E and Olson K B. *J Biol Chem* 122 153 1937
9. Jacques I B, Charles A F and Bick C H. *Acta med Scandinav (Suppl)* 90 190 1938
10. Bartlett M K, Jones C M and Bran, A L. *New England J Med* 226 460 1942
11. Alvarez W C. *An Introduction to Gastroenterology* ed 4 New York 1948 Paul B Hoeber Inc
12. Rigdon R H. *Proc Soc Exptl Biol*
13. Jaquet I B
14. Fote N C. *P*
15. Gehrmann G H. *J Urol* 31 1-6 1934
16. Pichard R K. *Science* 97 313 1947

VARIATIONS OF THE THORACIC DUCT

PAUL A VAN PERNIS MD GRAND RAPIDS MICH

(From the Butterworth Hospital)

THE thoracic duct is a poorly known structure in the human body. Indeed not all medical students have seen it nor observed its course upon the completion of their anatomy courses. Little has been written about it since the time of Hunter and Cruikshank about 1800. Those papers which have been written have been mainly descriptions of damage to the duct following trauma or observations made during thoracic surgery.

The philosophy of Galen as translated by William Cruikshank seems to have prevailed since the publication of his book in 1786*. Galen wrote "There is a certain length to which we may carry our researches but if we attempt to go beyond that, we shall soon convince ourselves that we neither understand our own imbecility, nor the great ability of Him who made us."

The following observations were made at post mortem examinations over a period of five years and since numerous variations from the classical descriptions were found it is deemed necessary that they be described.

METHODS

After the body has been opened by the usual Y shaped incision and the abdominal contents examined in situ the bowel is removed from the ligament of Treitz caudad. The costal cartilages are next cut through and the thoracic viscera examined in situ. The position of the superior surface of the aortic arch is then determined in relation to the thoracic vertebral bodies. The large vessels to the neck are then ligated, severed and the entire contents of the thorax and abdomen removed en bloc. The azigos veins are then opened and examined from behind. The thoracic duct is then found and dissected out, also from behind. The entire course, its branches, length and diameter, may then be determined and related not only to adjacent soft tissue structures but also to the spinal column by measuring first the duct and then the vertebral column beginning from the reference point where the arch of the aorta was before removal from the body. The superior portion of the thoracic duct may be examined during the course of the neck dissection. The skin and subcutaneous tissues are reflected cephalad exposing the neck anteriorly at least to the larynx. The clavicles are freed from the attached muscles and fascia and reflected to either side so that dissection of the structures beneath them is easily done. Thus the entire course of the thoracic duct and the receptaculum chyli become available for examination. Following this the examination of the remaining structures is done from behind insuring system continuity in the post mortem examination.

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Cruikshank William. The Anatomy of the Absorbing Vessels of the Human Body
London 1786

In this study 1 081 cadavers were examined. Some examinations had to be made after arterial injections by the embalmer, but this did not affect our study appreciably. Of 1 081 cases 386 or 35.6 per cent, were embalmed prior to examination.

FINDINGS

The length of the thoracic duct varied from 36 to 45 cm. as measured from the upper margin of the receptaculum chyli to its entrance into the subclavian vein. The beginning, or upper boundary, of the cisterna chyli was at the level of the twelfth dorsal vertebra in 111 cases, at the level of the first lumbar vertebra in 360 cases, and at the level of the second lumbar vertebra in 610 cases.

The thoracic duct in all 1 081 cases coursed through the aortic hiatus between the aorta andazygos vein. The site of crossing from right to left was at the level of the fifth thoracic vertebral body in 480 cases and at the level of the sixth thoracic vertebral body in 601 cases. It or its variations then entered the superior mediastinum on the left side behind the aortic arch and subclavian artery, between the left side of the esophagus and left parietal pleura to the upper orifice of the thorax. Single ducts were found in 663 or 61.3 per cent of the cases. Two or more branches of variable length were observed in 418 or 38.7 per cent of the cases. The variations in length and number of branches are given in Table I.

The caliber of the single thoracic ducts found varied from 2 to 4 mm. 421 cases were 2 mm. in diameter, 201 cases were 3 mm. in diameter and 41 cases were 4 mm. in diameter. Below the level of the eighth dorsal vertebra the thoracic duct was always a single duct. Pathologic lesions were found in only fourteen cases, an incidence of 1.3 per cent, and these were all found between the sixth and eighth vertebral body levels. Nine of these were tuberculous lesions, one a fungus lesion in which the yeast was seen intracellularly but not identified by culture because of prior embalming, two were metastases from uterine carcinomas, two from rectal carcinomas, and one from extensive melanocarcinoma of the vulva.

The right thoracic duct was identifiable in sixty-one cases of the total and always joined the left thoracic duct between the second and third dorsal vertebra level.

From the upper orifice of the thorax the combined or main thoracic duct arched 3 to 5 cm. above the clavicle crossing anterior to the subclavian artery in 892 or in 92 per cent of the cases and in the remainder it crossed posteriorly. It was always anterior to the vertebral artery and vein and the thyrocervical trunk, lying in front of the phrenic nerve and medial to the scalenus anterior muscle. The duct ended in the angle or within 1 cm. of the angle formed by the junction of the left subclavian and left internal jugular veins.

The position and number of valves observed in the course of the thoracic duct are markedly irregular and without any constancy except for a terminal valve which may be found at any position in the last 1 cm. of the duct.

TABLE I. VARIATIONS IN THORACIC DUCT

VARIATION	NUMBER OF CASES
<i>Bifurcated</i>	
For One Vertebral Body Length	
From 1st to 2nd thoracic	17
From 2nd to 3rd thoracic	20
From 3rd to 4th thoracic	21
From 4th to 5th thoracic	7
From 5th to 6th thoracic	3
From 6th to 7th thoracic	2
	70
For Two Vertebral Body Lengths	
From 1st to 3rd thoracic	4
From 2nd to 4th thoracic	22
From 3rd to 5th thoracic	16
From 4th to 6th thoracic	11
From 5th to 7th thoracic	3
From 6th to 8th thoracic	1
	58
For	
From 4th to 7th thoracic	2
From 5th to 8th thoracic	0
	2
For Four Vertebral Body Length	
	29
	4
	1
	41
For Five Vertebral Body Lengths	
From 1st to 6th thoracic	0
From 2nd to 7th thoracic	8
From 3rd to 8th thoracic	1
	12
No Bifurcations of Greater Lengths Were Found	
<i>Three Branches</i>	
None of Only One Vertebral Body Length Was Found	
For Two Vertebral Body Lengths	
From 1st to 3rd thoracic	0
From 2nd to 4th thoracic	0
From 3rd to 5th thoracic	3
From 4th to 6th thoracic	4
From 5th to 7th thoracic	0
From 6th to 8th thoracic	0
For Three Vertebral Body Length	
From 1st to 4th thoracic	1
From 2nd to 5th thoracic	4
From 3rd to 6th thoracic	4
From 4th to 7th thoracic	0
From 5th to 8th thoracic	0
	21
For Four Vertebral Body Length	
From 1st to 5th thoracic	7
From 2nd to 6th thoracic	13
From 3rd to 7th thoracic	0
From 4th to 8th thoracic	2
	22

TABLE I--CONT'D

VARIATION	NUMBER OF CASES
For Five Vertebral Body Lengths	
From 1st to 6th thoracic	1
From 2nd to 7th thoracic	3
From 3rd to 8th thoracic	5
	9
Those With Three Branches of Longer Length (one of even and two of ix)	3
	3
<i>Multiple Branches</i>	
One Vertebral Body Length	0
Two Vertebral Body Lengths	6
Three Vertebral Body Lengths	11
Four Vertebral Body Lengths	13
Five Vertebral Body Lengths	31
Six Vertebral Body Lengths	7

SUMMARY

The course and variations of the thoracic duct as observed in 1081 post mortem examinations are described. There are many more variations than are commonly recognized. Pathologic findings were observed in only fourteen cases. The thoracic duct is always a single duct from the level of the eighth vertebral body to the cisterna chyli which fact is of importance to thoracic surgeons particularly. The right thoracic duct is not easily demonstrable. Perhaps we have convinced ourselves. That we neither understand our own imbecility nor the great ability of Him who made us.

NEW TECHNIQUE AND GUIDE FOR ANGIOSTOMY

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FREQUENTLY in investigative work it is desirable to obtain blood repeatedly from an internal vessel not accessible to the usual methods of venepuncture. Procurement of such blood has required either an operative approach, sacrifice or previous operation to reroute a vessel near the body surface. The first two entail alteration of physiologic conditions as well as not allowing repeated determinations over a period of weeks or longer. The latter is often technically difficult or impossible. The purpose of this report is to describe a new type guide with which blood may be easily obtained from internal vessels many times over long periods during which time the animal has minimal physiologic alteration.

In 1935 London¹ prepared dogs and obtained blood from internal veins utilizing a two stage procedure. The first stage consisted of production of chemical and mechanical trauma to the venous wall and perivenous tissue in order to produce fibrosis. Several weeks later at the second stage a guide or cannula was sutured to this fibrotic area. Since the inner or attached end was sutured to or near a vessel it was always possible that blood obtained was not from this intended vein but from another near by. Nevertheless the apparatus has been used successfully by various investigators. Fig. 1 shows this type apparatus as used in a one stage procedure by Dent and Schilling.² Hamilton, Woodbury, and Vogt³ have used another modification whereby the entire apparatus is buried beneath the skin surface, the distal end consisting of a base plate sutured to perivascular tissue. Harrison and Tichow⁴ recently reported a buried polyethylene apparatus whose base is sutured to perivascular tissue. This has a polyethylene membrane across the distal end just at the vessel which is useful in fixing the penetrating needle in proper position and in acting as a tampon on the vessel wall when the needle is withdrawn.

These techniques have certain objectionable features. A guide which is not completely buried results in a sinus tract and infection about it. The externally protruding end necessitates added care of the animal. Even though the base plate of a guide is sutured securely near a vessel it may wander from the original site. Blood obtained via such an open ended tube may be from a different near by vessel which the penetrating needle has entered. In order to overcome these objectionable features a new type apparatus was designed and tested. This essentially is a metal guide fitted about the vein and extending from it to the subcutaneous tissue, the whole being beneath the skin surface. There are no sutures to vascular or perivascular tissue.

APPARATUS

Initially a crude model was made with tin shears, pliers, file and soldering iron using a tin can solder and a No. 17 needle (through whose lumen a No. 20

needle passes with ease) Since the result in one dog was excellent, the foreign body was well tolerated and blood was obtained with ease as frequently as desired the same materials were used further and plans to obtain Vitallium or tantalum guides were abandoned. The latter materials are less irritative to tissue but much more expensive. Fig 2 shows actual measurements of a guide successfully used about the portal vein.

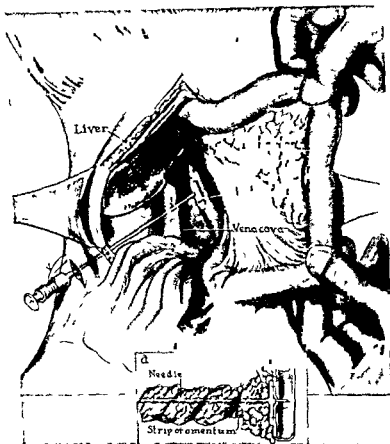


Fig 1—London type cannula sutured to portal vein. In *a* shows omental strip wrapped about this with venepuncture needle protruding through the guide into the portal vein. (From Dant and Schilling *Proc. Am. Soc. Clin. Path.* 1949)

The needle was chosen for length and cut across squarely on the end. The rounded $\frac{5}{8}$ circle end plate was then soldered to this by the projecting arm. The rounded $\frac{3}{8}$ circle base plate then slid about this easily with a protruding arm to attach to the needle component by ligatures. Besides these ties others about the ends of the enclosing base plate are tied so that a sturdy unit results.

PROCEDURE

Fig. 3 illustrates the guide in place about the portal vein projecting into the wound just prior to abdominal closure. In general the method of place-

ment was as follows. The operative approach was carried out on mongrel dogs under intravenous nembutal anesthesia supplemented by positive pressure machine oxygenation² when the chest was opened. The selected vein was gently dissected free for a sufficient distance to allow easy placement of the guide. Since several guides were available a selection was made prior to placement with particular regard to a natural position of the vein. The part of the guide with needle attached was initially placed after which the rounded base plate was slipped on and the two fixed together by ties as described. A site in the abdominal or chest wall was then selected on the basis of three criteria: (1) a position not in the operative wound; (2) a position which did not twist or kink the vein; and (3) a position where the head of the guide would be easily palpable and near a fixed landmark such as a rib or the wound scar itself. At this point

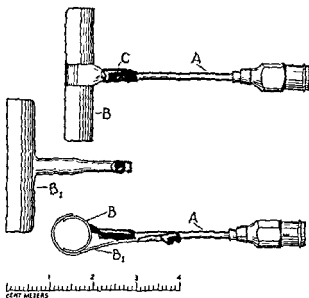


Fig. 1.—Specifications of a guide for portal vein cannulation. A, 17 gauge needle to which a circle tin with arm is soldered at C. B, 1 circle tin and plate with arm. Lower drawing shows an end view.

a small opening was made in the fascia and muscle and the head of the guide pushed through and fixed to the fascia by sutures from within so that the covering skin was never opened. The peritoneum or pleura was then closed about the guide with further sutures. In some instances it was feasible to dissect the skin fat layer from the fascia, bring the guide out of the fascia under direct view, and replace the flap as the wound was closed. After two sinuses had occurred this was abandoned. At the conclusion the needle head was always easily palpable and in most instances an immediate venipuncture was done in order to view directly the result. Occasionally this showed the internal needle to slide off the vein to one side when the guide about it was too large and loosely fitting. In this case substitution of a better fitting guide remedied the difficulty.

The wound was lastly closed in anatomic layers with interrupted fine silk sutures.

During and after wound healing the head of the guide was always palpable. After location a No. 20 gauge needle with indwelling stylet was passed through the skin and into the hub of the guide. This was definitely indicated by the metallic grating which occurred. In order to assure that the entering needle passed into the guide and not down its outside lateral bending of the entering needle in different directions was done as it was slowly introduced. Continuation of the metallic grating during this maneuver was indication of proper position. After this assurance the stylet was removed and with negative pressure from an attached syringe the venepuncture needle was slowly advanced into the guide until blood appeared or until the needle stopped when it reached the base plate. In case no blood was obtained the needle was withdrawn somewhat and the procedure repeated.

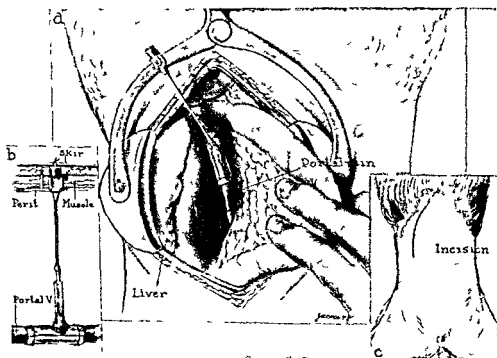


Fig. 3-4. (a) Guide in place about portal vein prior to closure of abdomen. (b) Fixation of needle hub to fascia and peritoneum. (c) Incision used.

RESULTS

Ten different guides were placed in four dogs; frequent venepunctures done and autopsy examination made in each case.

Four portal vein guides were uniformly successful except for one in which the guide was too short and continued to retract into the deep tissues so that it could not be palpated. No venepuncture was ever attempted in this one. Fig.

4 shows 70 per cent Diodrast injected via a guide on the portal vein outlining the portal venous system. Ten to fifteen cubic centimeters of blood were always obtained with ease and venepunctures through the guides were done frequently and repeatedly, up to thirty two times on a single vein. Two of the animals developed near by sinuses which never interfered with venepuncture. No other complications occurred. The three successful preparations were carried two, three and four months prior to autopsy examination.

The *vena cava* in its supradiaphragmatic portion was once prepared. This functioned well for thirteen days, at which time the dog was sacrificed. There was no complication.



Fig. 4.—X-ray visualization of portal venous system of dog after 70 per cent Diodrast injection into the portal vein through guide. Visceral tributaries lie to the right. To the left are intrahepatic portal division and their ramifications.

The right inferior pulmonary vein was prepared twice. The first animal died of bilateral pneumonia after twenty four hours and venepuncture was never attempted. The other functioned well and easily for twenty days after which function was absent and the animal died on the twenty fourth postoperative day with massive pericardial effusion. This was presumably due to irritation by the foreign body which indented and pressed on the pericardium.

The *splenic renal* and *mesenteric* veins were all used once. Venepuncture of these smaller veins was never very easy. No more than a few drops to $1\frac{1}{2}$ cc of blood were ever obtained from them. No complications resulted from the procedures.

The three complications which developed were due to foreign body, consisting of the mentioned death of pericardial effusion and two sinuses of the abdominal wall. At no time was there evidence of bleeding upon withdrawal of the venepuncture needle from the vein. This was attributed to the firm fibrosis which developed about the guide and vein and to soft granulations which extended into the lumen portion of the guide.

At secondary operation or at autopsy the constant finding was a tough dense mass of adhesions about the metal enclosing it in a fibrous sheath. Within the needle portion there were soft red friable granulations. Microscopic examination showed foreign body reaction and dense fibrosis. The enclosed vein was always thicker than usual with a tough whitish wall and decreased luminal size. Microscopically this apparently began as inflammation of the adventitia which spread through the wall with resultant scarring and fibrosis. Thrombosis occurred in the small veins only.

COMMENT

The following points are worthy of note

1 If the animal can reach the projecting end of the guide with his teeth he is likely to tear the skin over it. A different point should be selected or a protective coat kept on the animal.

2 A guide too long is better than one too short. The short one retracts and may be lost while the long one merely bulges the skin over it but is well tolerated beneath the freely movable skin.

CONCLUSION

A new apparatus and technique for procurement of internal venous blood is presented which is inexpensive, simply applied at a one stage operation and well tolerated for a considerable period by dogs.

REFERENCES

- 1 Dent C F and Schilling I A. *Biochem J* 44 318 1949
- 2 Gunkler W A and Mahoney F B. *Surgery* (To be published)
- 3 Hamilton W F, Woodbury P A and Vogt F. *Am J Physiol* 125 130 1939
- 4 Harrison W and Liebow A A. *Proc Soc Exper Biol & Med* 70 226 1949
- 5 London F. *Angiostomie und Organe toffwechsel* Moskau 1937, Des all union Instituts fur exper Med

PRODUCTION OF LESIONS OF THE GASTRODUODENAL MUCOSA BY FREQUENT SHAM FEEDING

DAVID C FAINER MS, MD, HENRY D JANOWITZ, MS, MD,
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(From the Department of Clinical Science University of Illinois College of Medicine)

SHAM feeding results in a high rate of gastric secretion by vagal stimulation. Hypersecretion is usually present in patients with duodenal ulcers. As one means of studying the importance of hypersecretion in the pathogenesis of peptic ulcers, it is reasonable to attempt to produce experimental ulcers by sham feeding.

The reports on attempts to produce peptic ulcers by sham feeding have been contradictory. For instance, Silbermann¹ found that 18 of 23 dogs developed ulcers of the stomach and duodenum after being sham fed three times a day for 14 to 49 days. Schmidt and Fogelson² repeated the experiment essentially as Silbermann had done. However, no ulcers or erosions were found in 5 dogs which were sham fed three times a day for 20 to 60 days. The findings of these and other authors are summarized in Table I.

In previous experiments sham feeding has been performed two or three times a day. It may be presumed that the stomach and duodenum were subjected to high levels of gastric secretion for only 2 or 3 hours with each sham feeding. Even then the gastric juice may have been buffered by a meal introduced into the stomach. This does not simulate adequately the continuous secretion particularly the night secretion of duodenal ulcer patients. Gastric and duodenal ulcers can be produced in dogs by the continuous intragastric infusion of acid or acid and pepsin^{3,4} but not by intermittent infusion.

The aim of this experiment was to expose the stomach and duodenum to relatively continuous hypersecretion by frequent sham feeding.

METHOD

Lophagostomies were produced in 16 dogs weighing 6.4 to 15.5 kilograms. The exteriorized esophagus was divided on the fifth postoperative day and the experiment began 10 days to 3 months postoperatively. Sham feeding was performed 5 to 24 times a day. The sham feeding diet consisted of a commercial dog food⁵ or raw or cooked horse meat.

All animals were sacrificed when they refused to sham feed for 4 to 6 consecutive hours. The development of a gastroduodenal lesion was felt to be the cause of cessation of sham feeding. The interval of 4 to 6 hours was chosen to prevent a significant degree of healing of the lesions.⁶

Food was withheld from 9 intact dogs for 10 days although water was given ad lib. These dogs served as controls to determine the effect of starvation on the stomach and duodenum.

Several different schedules of sham feeding and real feeding were used. All dogs received intragastric water or 0.3 per cent saline solution. Nine received one daily intragastric feeding of a homogenized mixture of milk and commercial dog food. This is summarized in Table II.

RESULTS

In the control group of 9 animals from which food was withheld for 10 days no ulcers or erosions were found in the stomach or duodenum. The duodenum of 8 dogs was hyperemic (Table III).

TABLE I PREVIOUS REPORTS ON THE PRODUCTION OF ULCERS BY SHAM FEEDING

AUTHOR	NO OF DOGS	DURATION OF EXPERIMENT (DAYS)	SHAM FEEDING SCHEDULE	FEEDING	RESULTS
Lanow	8	--	--	--	1 perforating GU 3 perforating DU
Silferrmann	3	14-19	3 times daily	--	15 ulcers of stomach and duodenum
Brenckman and White	10	14-84	2 to 3 times daily	--	0 ulcers some with gastritis and duodenitis
Pachner and Schneiders	11†	14	--	--	1 DU 3 with erosions
Pohl and Brodersen	1	3-14	--	--	0 ulcers some with gastritis and duodenitis
Schmidt and Fogel	5	10-60	3 times daily	Once daily by stomach tube	0 ulcers some developed duodenitis

† Five dogs sham fed poorly sacrificed after 10 to 13 days and no abnormality noted
† Four dogs sham fed poorly

TABLE II SCHEDULE OF EXPERIMENTAL PROCEDURES IN VARIOUS GROUPS OF SHAM FED DOGS

NUMBER OF DOGS	SHAM FEEDING		DIET	RESULTS
	SCHEDULE	NUMBER OF DAYS		
5	Every hour for 5 min	4 to 6½ days	None	Ulcer 1 hemorrhagic erosion 3 negative 1*
-	Every 2 hr for 10 min	7½ days	None	Ulcer 1 hemorrhagic erosion 1
4	Every 2 hr for 10 min	4½ to 8½ days	Once daily	Hemorrhagic erosion 1 negative 3
3	Five times daily ad lib†	4 days	Once daily	Submucosal hemorrhage 3
-	Five times daily ad lib†	11 days	Once daily	Ulcer 1 submucosal hemorrhage 1

* Food entered stomach with each sham feeding
† Allowed to sham feed until final feed

TABLE III INCIDENCE OF LESIONS IN SHAM FED DOGS AND FASTED CONTROLS

	TOTAL NO	ULCER	HEMORRHAGIC EROSIONS	SUBMUCOSAL HEMORRHAGE	ESSENTIALLY NEGATIVE
Controls	9	0	0	0	9
Frequent sham feeding	11	1	5	4	4

Intact dog not fed for 10 days

TABLE IV CORRELATION OF AVILITY OF SHAM FEEDING WITH LESIONS FOUND AT NECROPSY

AVILITY OF SHAM FEEDING	NO OF DOGS	LESION			
		ULCER	EROSION	SUBMUCOSAL HEMORRHAGE	NEGATIVE
Vigorous	6	3	1	0	-
Fair	3	0	-	0	1
Poor	1	0	-	4	1

(One dog had food enter stomach with each sham feeding and the other dog had more than 9 hours gastric retention of food)

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All animals were sacrificed when they refused to sham feed for 4 to 6 consecutive hours. The development of a gastroduodenal lesion was felt to be the cause of cessation of sham feeding. The interval of 4 to 6 hours was chosen to prevent a significant degree of healing of the lesions.⁵

Food was withheld from 9 intact dogs for 10 days although water was given ad lib. These dogs served as controls to determine the effect of starvation on the stomach and duodenum.

Several different schedules of sham feeding and real feeding were used. All dogs received intragastric water or 0.3 per cent saline solution. Nine received one daily intragastric feeding of a homogenized mixture of milk and commercial dog food. This is summarized in Table II.



Fig. 2.—Photomicrograph of acute peptic ulcer shown in Fig. 1 demonstrating penetration of the muscularis mucosa and overhanging edge.

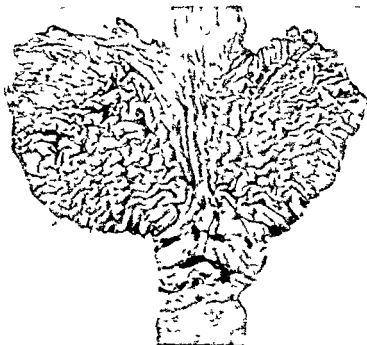


Fig. 3.—Acute hemorrhagic antral erosions produced by frequent sham feeding for 7 days.

Of 16 dogs which were sham fed frequently for 4 to 11 days 3 developed acute peptic ulcers 9 developed hemorrhagic erosions or submucosal hemorrhage in the stomach, and 4 had essentially normal gastroduodenal mucosa (Table III)

The acute ulcers were located at the pylorus and the edges were overhanging (Fig 1). Microscopically the ulcers penetrated the muscularis mucosa (Fig 2). Hemorrhagic erosions appeared most frequently in the pyloric antrum (Fig 3) although fundic erosions also occurred. Microscopically, these did not penetrate the muscularis mucosa.

Before necropsy was done on each animal the over all avidity of sham feeding was estimated. The avidity of sham feeding was correlated with the severity of the lesion found. The results are shown in Table IV. The most severe lesions were produced in animals which sham fed vigorously.



Fig 1—Acute peptic ulcer at the pylorus produced by frequent sham feeding for 4 days. This lesion was 8 mm in diameter.

Gastric acidity was determined at intervals following sham feeding in many dogs. When sham feeding was vigorous the mean free gastric acidity at one hour was 88 mN units (range 48 to 132 mN) at 2 hours 81 mN (range 48 to 110 mN) and at 3 hours 50 mN (range 34 to 76 mN). When sham feeding was only fair the mean free gastric acidity at one hour was 76 mN (range 18 to 55 mN). When sham feeding was poor the mean free gastric acidity at one hour was 28 mN (range 0 to 48 mN).

The results indicate that the buffering activity of food introduced into the stomach caused some decrease in the number of ulcers and other lesions but not to a statistically significant degree. Nine dogs were fed through a



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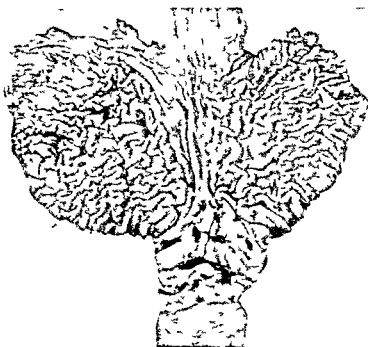


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A RESPIRATOR FOR USE IN INTRATHORACIC SURGERY IN THE DOG

WALTER A. GUNKLER, M.D. AND EARLE B. MAHONEY, M.D. ROCHESTER, N. Y.
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INTRODUCTION

DURING the past three years we have been attempting various intrathoracic surgical procedures on the dog. Our first attempts were markedly handicapped by lack of satisfactory anesthesia. Deliberate meticulous surgery was prevented by the difficulty in maintaining respiratory exchange with an opening in the pleura large enough for adequate exposure. We have developed a method and an apparatus which we believe eliminates this difficulty.

Quenu and Longuet¹ in 1896 described a method of encasing the head of a dog in a rubber sac sealing it about the neck and rhythmically compressing the sac in order to create a positive pressure. They used chloroform for an anesthetic agent. In the same year Tuffier and Halhon described a method of blowing air into an intratracheal tube by means of a bellows. Matas² in 1899 described the Fell O'Dwyer apparatus which was a bellows arrangement for insufflating the trachea. Murphy³ in 1905 described 'A Practical Apparatus For Use in Intrathoracic Operations'. This apparatus consisted of a box into which the head of the animal and the hands of the anesthetist were introduced and sealed in with rubber cuffs. The anesthetist operated a foot pump which pumped air through an ether bottle and then into the box. Sauerbruch⁴ in 1904 described a chamber in which the patient and operators were placed, a negative pressure being maintained within the chamber. The constant negative pressure was supposed to keep the lung of the patient constantly expanded. In 1909 Meltzer and Auer⁵ described a method of continuous respiratory movements which according to Cutler superseded all previous methods of maintaining respiratory exchange in an animal with an open thoracotomy. As originally described the method of Meltzer and Auer depended on placing in the trachea through a tracheotomy an intratracheal tube. The outside diameter of this tube was smaller than the lumen of the trachea. A continuous flow of air passed first through an ether bottle and then into the intratracheal tube. Pressure was maintained at 20 mm. of mercury. The essential point of the arrangement was that the air which was introduced into the intratracheal tube escaped around the tube and out through both the tracheotomy and the larynx. The Meltzer-Auer method was modified subsequently to employ laryngeal intubation rather than tracheotomy. Pierce⁶ in 1923 described an 'Artificial Respiration and Fiber Apparatus for Use with Compressed Air'. This apparatus intermittently interrupted a stream of air passing through an ether bottle by

stomach tube once daily. Six developed lesions of varying degree of which one was an ulcer. Seven dogs were given only dilute saline solution. Six developed lesions of varying severity of which 2 were ulcers (Table II).

Peptic ulcers produced by sham feeding have been said to be the result of starvation.² However no significant lesions developed in 9 control dogs which were starved for 10 days. In dogs which were sham fed the percentage body weight loss was calculated from the preoperative weight and the necropsy weight. Dogs which developed no lesions had a mean body weight loss of 11.9 per cent (range 0 to 17.6 per cent). Dogs which developed submucosal hemorrhage had a mean body weight loss of 20.4 per cent (range 13.6 to 29.0 per cent). Dogs which developed hemorrhagic erosions had a mean body weight loss of 11.3 per cent (range 0 to 17.6 per cent). Dogs which developed ulcers had a mean body weight loss of 12.1 per cent (range 9.7 to 13.6 per cent). Starvation and malnutrition do not appear to be the primary factor in the production of peptic ulcers by sham feeding, but may play a role.

DISCUSSION

Prolonged intense continuous physiologic vagal stimulation produced by sham feeding can under the conditions of this experiment lead to injury of the gastroduodenal mucosa. This suggests the possibility that similar factors may operate in the human peptic ulcer patient. However despite claims to the contrary the question of the existence of vagal hyperactivity in human ulcer patients cannot be considered to be settled. As we have pointed out elsewhere¹⁰ further evidence is needed. Therefore the application of the findings of this study to the human disease must await further study.

SUMMARY

Continuous gastric hypersecretion in the dog has been produced by frequent sham feeding. Of 16 dogs peptic ulcers developed in 3 and erosions or submucosal hemorrhages in 9 after 4 to 11 days of frequent sham feeding.

REFERENCES

1. Silbermann I. S. Experimentelle Magen-duodenal-ulcer-erzeugung durch Scheinfuttern nach Pavlov. *Zentralbl. f. Chir.* 64: 345, 1947.
2. Schmidt C. R. and Fogelson S. J. The Effect of Physiologic Hypersecretion on the Gastro-duodenal Mucosa: An Experimental Study in the Dog. *Am. J. Physiol.* 120: 87, 1945.
3. Janowicz N. Ulcus rotundum ventriculi. *Zeitschr. f. d. Grenzgeb. d. Med. u. Chir.* 23: 318, 1899. (Abstract from Die Jurgens 1949.)
4. Brexelman F. and White J. Influence des repas fictifs et du regime ave et sans la chien. *Arch. le mal de l'app. digestiv*
rimente zur Entstehung, 14 peptischen
der ulcera in tra tritis und Duodeniti
die Einwirkung, artemigena Magensaft
f. Klin. Chir. 68: 311, 1906.
5. Grossman M. I. An Experimental Study of the
Acid Factor in Ulceration of the Gastrointestinal Tract in Dogs. *Gastroenterology*
10: 714, 1948.
6. Fogelman M. J., Grossman M. I. and Janowicz N. Further Studies on the Effect of
Continuous Intra-gastric Infusion of Acid and Pepsin in Dogs. *Surgery* 25: 10, 1949.
7. Grant P. Rate of Replacement of the Surface Epithelial Cells of the Gastro-mucosa.
Anat. Rec. 91: 110, 1945.
8. Grossman M. I. Is the Hypersecretion Observed in Duodenal Ulcer Entirely Due to
Excessive Vagal Stimulation of the Stomach? *Gastroenterology* 13: 91, 1949.

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INTRODUCTION

DURING the past three years we have been attempting various intrathoracic surgical procedures on the dog. Our first attempts were markedly handicapped by lack of satisfactory anesthesia. Deliberate, meticulous surgery was prevented by the difficulty in maintaining respiratory exchange with an opening in the pleural space enough for adequate exposure. We have developed a method and an apparatus which we believe eliminates this difficulty.

Quenu and Longuet¹ in 1896 described a method of encasing the head of a dog in a rubber sac sealing it about the neck and rhythmically compressing the sac in order to create a positive pressure. They used chloroform for an anesthetic agent. In the same year Tuffier and Hallion² described a method of blowing air into an intratracheal tube by means of a bellows. Mats³ in 1899 described the Fell O'Dwyer apparatus which was a bellows arrangement for insufflating the trachea. Murphy⁴ in 1905 described 'A Practical Apparatus for Use in Intrathoracic Operations'. This apparatus consisted of a box into which the head of the animal and the hands of the anesthetist were introduced and sealed in with rubber cuffs. The anesthetist operated a foot pump which pumped air through an ether bottle and then into the box. Sauerbruch⁵ in 1904 described a chamber in which the patient and operators were placed, a negative pressure being maintained within the chamber. The constant negative pressure was supposed to keep the lung of the patient constantly expanded. In 1909 Meltzer and Auer described a method of continuous respiratory movements which according to Cutler superseded all previous methods of maintaining respiratory exchange in an animal with an open thoracotomy. As originally described the method of Meltzer and Auer depended on placing in the trachea through a tracheotomy an intratracheal tube. The outside diameter of this tube was smaller than the lumen of the trachea. A continuous flow of air passed first through an ether bottle and then into the intratracheal tube. Pressure was maintained at 20 mm. of mercury. The essential point of the arrangement was that the air which was introduced into the intratracheal tube escaped around the tube and out through both the tracheotomy and the larynx. The Meltzer-Auer method was modified subsequently to employ laryngeal intubation rather than tracheotomy. Pierce⁶ in 1923 described an 'Artificial Respiration and Ether Apparatus for Use with Compressed Air'. This apparatus intermittently interrupted a stream of air passing through an ether bottle by

means of a compressed air motor operating a valve. Mautz⁹ in 1939 described a mechanical respirator as an adjunct to anesthesia, and in 1940¹⁰ described an improved apparatus which could be integrated with the common closed system gas anesthesia machines. This apparatus provided for rhythmic compression of a rebreathing bag connected to the patient and to the anesthesia machine. The rebreathing bag was contained in a transparent chamber into which compressed air was intermittently introduced. This apparatus is now commonly used in human thoracic surgery.

The Meltzer-Auer method in our hands was unsatisfactory for the type of surgery we wanted to do. We found it difficult to maintain a proper depth of anesthesia; respiratory struggling was marked and death of the animal frequently resulted. The apparatus described by Pierce was also unsatisfactory in our hands. With this apparatus a trained anesthetist was unable to maintain surgical anesthesia without anoxemia. Surgery was necessarily hurried and the operator was constantly working against time. The Mautz respirator although most satisfactory for human surgery did not appear practical for use in the laboratory because of the amount of equipment required. Furthermore we wanted some system which did not require the services of a trained anesthetist.

APPARATUS

Sodium pentobarbital or nembutal administered intravenously is a very satisfactory anesthetic agent in the dog. In abdominal surgery we have used it some 100 times with a mortality rate from anesthesia of under 3 per cent.¹¹ The deaths which did result were almost always from overdose by an inexperienced technician. On the basis of this experience it seemed desirable to use nembutal as an anesthetic for thoracic surgery and to construct a respirator* the sole function of which would be to maintain respiratory exchange.

Fig. 1 shows a diagram of the respirator. An oxygen tank is equipped with an ordinary Venturi gauge calibrated for flow in liters per minute. The oxygen flows through the respirator to the outlet which is connected with an intratracheal catheter. The flow is interrupted 20 times per minute by a solenoid activated gas valve. The valve is operated by an electric timing motor. When the valve is closed the oxygen flowing into the respirator must escape through the outlet and into the intratracheal tube. When the valve is open the oxygen flows directly through the line to the exhaust and is lost to the outside air. During this same phase that is when the valve is open expired air will escape from the lungs through the intratracheal tube and out the exhaust.

It should be noted that no provision is made for suction during the expiratory phases. Mautz¹⁰ has pointed out that suction is not a desirable function of a respirator.

The timing motor is a 110 volt 60 cycle A.C. motor with a gear reduction box. The essential feature of the timing motor is an exposed brass timing gear which revolves ten times per minute. The magnetic valve is wired in series with this gear and the circuit is made and broken by means of a contact brush. Por-

*The respirator was designed and constructed in cooperation with Mr. John W. Armstrong of Rochester, N. Y.

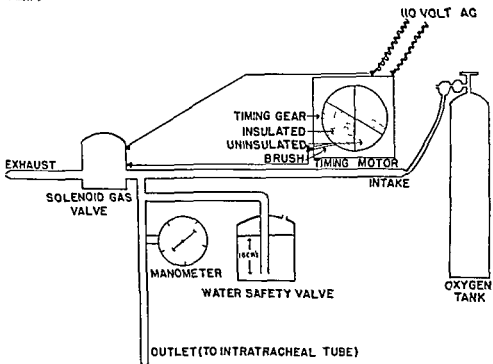


Fig 1—Diagram of respirator

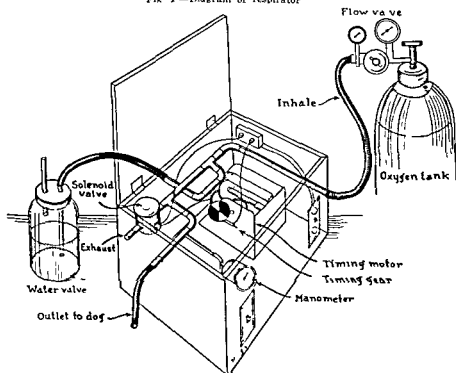


Fig —Drawing of respirator

tions of the face of the gear are insulated in such a way that as the gear revolves, contact is made by the brush for one second and broken for two seconds. Making contact activates the solenoid in the valve and opens it. Breaking contact allows the valve to close.

We have used a maximum pressure within the system of 10 cm. of water. A safety valve is incorporated in the respirator which blows off if a pressure higher than this is created. This safety valve consists of sidearm submerged to a depth of 10 cm. in water. Pressures lower than this can be obtained by diminishing the rate of flow at the tent valve.

An aneroid manometer is incorporated in the respirator so that the pressure obtained at any given moment is visible.

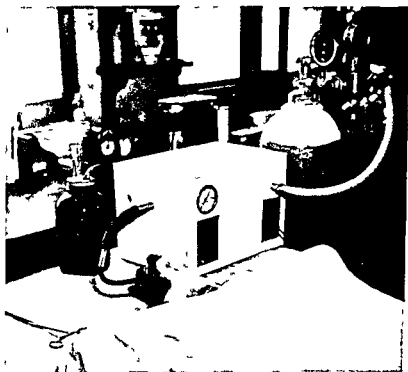


Fig. 3—Photograph of respirator

The respirator is constructed from easily available material. The tubing is ordinary one half inch galvanized water pipe with ordinary plumbing T's and F's. The magnetic valve had been in use for several years on an automatic gas hot water heater. The timing motor was one which was originally used to time the opening and closing of a steam radiator. The manometer was purchased commercially. The entire apparatus with the exception of the safety valve, is enclosed in a wooden box 10 by 12 by 14 inches.

METHOD OF OPERATION

The method of operation is quite simple. The dog is strapped supine on the operating table. A superficial vein in the hind leg is selected and a solution of nembutal containing 60 mg. per cubic centimeter is injected. In general, 32 mg. per kilogram of body weight is required but there is wide individual variation from this in either direction. Our technique is to inject very slowly until the reflexes are lost and the respirations are slow and regular. We then stop the injection and give no more until indicated. When surgical anesthesia has been obtained the needle in the vein is connected to a constant drip of Ringer's solution. A No. 24 Foley catheter with the blind end cut off is then put in the trachea and the bulb inflated. Intubation of the dog's trachea is simple. Extension of the head and traction on the tongue yields a clear view of the epiglottis. When the epiglottis is lifted the vocal cords are exposed and the catheter can be slipped in without difficulty. The dog is placed in the desired position for surgery and the operation started. Just before the pleura is to be opened the intratracheal tube is connected to the respirator and the oxygen flow started.

Fig. 2 is an artist's drawing of the apparatus. Fig. 3 is a photograph of the apparatus in use.

Sodium pentobarbital is a respiratory depressant. This seems to be an advantage when the respirator is used since almost without exception once the dog is on the respirator he makes no voluntary respiratory efforts. During a long operation additional nembutal must be injected. Indications for this are swallowing, struggling or respiratory efforts. Recently we have been using Intocostrin in conjunction with the nembutal and this may prove to be of value in accomplishing a smoother anesthesia.

RESULTS

Using the respirator we have carried out open thoracotomies on over fifty dogs resecting usually the seventh rib and opening the pleura wide enough to give adequate exposure. These thoracotomies have been done for lobectomy, division and reanastomosis of the thoracic aorta, anastomosis of the subclavian artery to the pulmonary artery and cannulation of the thoracic duct. The pleura has been open in these operations for an average of from two to three hours. We have kept the pleura open for as long as six hours in order to test the efficiency of the method and the apparatus. We have had no fatalities which we considered attributable to the anesthesia.

We have encountered no complications from the contact of the Foley bulb with the trachea although it is realized that mild degrees of tracheitis would be difficult to recognize in a dog.

In all the operations the operator was able to dismiss anesthetic problems from his mind. He was able to carry out the surgical procedure with all the deliberateness that he desired.

The respirator is entirely automatic and will run for as long as is desired without attention. Additional pentobarbital can be injected when necessary by any laboratory technician acting as circulating nurse.

None of the dogs had more than minimal bronchial secretion. Bronchoscopy was carried out routinely at the close of each operation but usually proved unnecessary. In two cases when the chest was closed and the respirator shut off, the animal did not breathe spontaneously. In each of these cases the dog was put back on the respirator with a 90 per cent oxygen—10 per cent CO₂ mixture for five minutes and spontaneous respirations then began. In one case satisfactory anesthesia could not be obtained with nembutal. When the initial dose was injected the dog developed shallow jerking respirations which could not be eliminated. This dog later showed the same reaction when anesthetized with nembutal for an abdominal operation.

IMPROVEMENTS

Several improvements in the respirator are contemplated and we are now constructing a model incorporating them. *One* A three way solenoid valve will be used to eliminate the waste of oxygen. *Two* Sparking within the respirator will be eliminated by using a mercury tumbler switch tripped by a cam. *Three* A smaller safety valve will be used employing a commercial type diaphragm valve. *Four* Adjustment of the respiratory rate and of the inspiration expiration ratio will be made possible.

CONCLUSIONS

For intrathoracic surgery in the dog we have used intravenous nembutal for anesthesia. We have designed a simple respirator which is easily constructed from readily available material. In our hands the method has proved most satisfactory and is superior to any other method we have used. Improvements in the respirator will be made.

REFERENCES

- 1 Quenu and Longuet. Note sur quelques techniques experimentales concernant la chirurgie thoracique compl. rend Soc de Biol 3 1897 1898
- 2 Tuffier J and Hallion. Operations intrathoraciques avec respiration artificielle par insufflation. Compt rend Soc de Biol 3 jan 1936
- 3 Matisa Rudolph. On the Management of Acute Traumatic Pneumothorax. Ann Surg 29 428 1899
- 4 Murphy Fred T. A Suggestion for a Practical Apparatus for Use in Intrathoracic Operations. Boston M & S J 182 48 1906
- 5 Sauerbruch F. Ueber die Physiologie und die klinischen Grundlagen der intra-thorakalen Eingriffen in meiner Pneumothorax-Operationen. Arch f klin Chir 73 917 1904
- 6 Meltzer H J and Auer Julia. Continuous Respiration Without Respiratory Movements. J Exper Med 11 6-2 1909
- 7 Cutler, Elliott C, Levine Samuel A and Berk Claude S. The Surgical Treatment of Atrial Septal Defect. Arch Surg 6 62 1934
- 8 and Fisher Apparatus for Use With Commercial Artificial Pulmonary Ventilation in the Operative. 1939
- 9 Artificial Pulmonary Ventilation in the Operative. 1940
- 10 Walter A and Kingley H D. The Role of Oxygenation. (To be published)

COTTON AS SUTURE MATERIAL IN UROLOGIC SURGERY

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IN OUR graduate training in general surgery we had been taught silk technique and of course were convinced of its superiority over catgut in uncontaminated wounds. In urologic surgery therefore we used silk in operations upon the scrotal contents but feared to apply it to surgery of the urinary tract because troublesome silk suture granulomas were to be expected.

The medical literature is rife with articles on the disadvantages of catgut suture material which we may briefly summarize. Its rate of absorption is variable and is accelerated by infection and the presence of urine. Because of the inflammatory reaction which it incites in tissue fibroplasia is delayed. When it is used in grossly contaminated wounds close to 100 per cent of cases will develop infection. Since no wound is strictly sterile a significant number of "clean" wounds will become infected when the excessive inflammation caused by catgut develops. Because this is true it is the rule for urologic surgeons to place drains in most wounds whether grossly contaminated or not. The use of drains can only increase the incidence of infection.

Since catgut has a low coefficient of friction knots under tension are not secure and since this material is not pliable knots cannot be brought down "tight." Catgut swells when buried in tissue and unless the ends of the sutures have been left long there is a tendency for these knots to untie spontaneously. This is particularly true if doubled catgut sutures are used. The tensile strength of catgut is lost rapidly and it is weak before adequate fibroplastic proliferation has developed. The only advantage that catgut could have over nonabsorbable sutures is the absence of troublesome sinus formation or foreign body granulomas. It is not uncommon however for catgut knots to be extruded from wounds a few weeks after their placement.

When the use of cotton sutures was popularized by Meade and Ochsner and others and evidence accumulated that sinuses and granulomas were rare or nonexistent when cotton was used we decided to use it in operations upon the urinary tract. Cotton is easily sterilized. It excites little inflammatory reaction so fibroplasia appears early and progresses rapidly. It has been demonstrated that many contaminated wounds will heal without infection when fine cotton sutures are used. Clean wounds may be expected to heal per primam and therefore need not be drained. Cotton maintains its tensile strength well beyond the time that firm healing of the wound has taken place and because of its high coefficient of friction and its pliability knots can be tied tightly and they will remain so. All authorities however stress the need for careful technique when cotton is used.

The only disadvantage to the use of this material is the possibility that the buried cotton may act as a foreign body with the formation of sinuses or granulomas. First reports denied this but a few have recently appeared which admit of a number of late complications due to the cotton itself.

Two papers have appeared in the urologic literature which discuss experiences with cotton sutures and we have a personal communication from Nesbit concerning his results with this material. Bernardi and Macchi in 1943 reported on the use of cotton sutures in forty-four patients. Twenty-one of these were aseptic operations applied to the serotal contents. They noted that healing was excellent and that extrusion of cotton sutures was rare. Cotton sutures were also used in twenty-three wounds which they considered to be contaminated. These included such operations as prostatectomy, pyelolithotomy, nephrectomy, and drainage of abscesses. These authors were discouraged with the results in this group. Healing occurred by secondary intention and this took longer than if catgut had been used. Extrusion of cotton was the rule even months after the wounds were healed. They felt that cotton sutures despite the claims of other authors do harbor bacteria when bathed with infected urine and finally extrude themselves and concluded that the use of cotton sutures is contraindicated in contaminated wounds.

In contradistinction to this, Melick in 1946 reported upon his experience with cotton in thirty-two cases. Drains were left in the wounds for as long as four days. He noted no complication whatever, no sinuses or extrusion of sutures, no induration of the wounds, no disruptions and no hernias.

Nesbit employed cotton routinely some years ago and at first was much impressed by the uniformity of primary healing which he obtained. But 'after we had been employing cotton for a period of seven or eight months patients began to return complaining of draining wound sinuses and upon investigation it was found that a majority of these cases had healed per primam but after several weeks or months had developed small tender soft areas in the scar which eventually broke down. Cotton material extruded spontaneously from some but in the majority the sinuses continued to drain until surgical removal was effected.' This experience caused him to cease using cotton suture material.

Our series was started in April 1942 and was closed at the end of 1946 in order to allow a minimum of two years for follow-up. Sharp dissection was used routinely at first but in 1943 we began to incise the lumbar muscles with the electrosurgical scalpel and to coagulate the smaller bleeders. Larger vessels were tied or transected with No. 40 or 60 cotton. The use of fine pointed clamps, fine Ferguson and French eye needles, light forceps and the insistence upon careful hemostasis were stressed. Wounds were closed without drainage unless urine was expected to drain or gross contamination of the wound was present. Closure of muscles and fascia was accomplished with figure of eight doubled No. 40 cotton sutures. Interrupted No. 60 cotton sutures were used in the subcutaneous tissue and skin.

At the outset cotton sutures were used exclusively in all wounds except where they might penetrate the mucosa of the urinary tract. Here 000 or 0000 plain catgut was used. Renal vascular pedicles clamped en masse were tied or

transfixed with double No 1 chromic catgut rather than with cotton for fear the finer cotton might cut through the vessels

This series is comprised of 196 cases and the majority of the patients were operated upon by eight members of the resident staff at the University Hospital. Of this group, 142 were classified as "clean", 78 of these involved the upper urinary tract and included the removal of 53 kidneys most of which were infected. They were "clean" because the pelvis or ureter was not opened (Table I). Complications in this uncontaminated group included five wound infections. Two developed following lumbar nephrectomy, one of these was mild and superficial while the other proved to be a deeply placed infected hematoma requiring surgical drainage. Of the fifteen nephrectomies performed through a transperitoneal approach one became superficially infected following radiation therapy to the area and four cotton sutures were extruded spontaneously during the subsequent four weeks. The wound of one patient subjected to exploratory laparotomy discharged one cotton suture two months after operation though the wound healed per primam. A similar episode occurred following excision of a solitary cyst done through a lumbar incision. Six months later, a small but definite hernia could be demonstrated in this wound though gross infection was never present. Following transperitoneal exploration and excision of a solitary cyst of the kidney excoriation occurred in one instance and the wound was immediately closed with through and through silver wire sutures. No hernia developed nor were cotton stitches ever extruded. Only one mild wound infection developed following the operations upon the external genitals and this healed readily without complication.

Of the seventy eight patients undergoing clean surgery of the upper urinary tract then only three or 3.8 per cent spontaneously discharged cotton from the wound, and two of these occurred late from incisions which seemed to have

TABLE I UNCONTAMINATED WOUNDS

OPERATION	NUMBER	CLOSED WITHOUT DRAINAGE	WOUND INFECTIONS	COTTON EXTRUSION
Exploratory laparotomy	9	9		1 case 1 knot at 2 months
Excision of solitary cyst trans peritoneal	2	0	1 Excoriation	
Excision of horseshoe kidney	1	1		
Excision of solitary cyst lumbar approach	3	0		1 case 1 knot at 5 months
Nephropexy	7	~		
Nephrectomy for cancer	1	1		
Nephrectomy lumbar approach	38	33	1 Superficial 1 Deep	
Nephrectomy trans peritoneal	10	14	1 Superficial	1 case for 1 month following x ray
Uretero sigmoidostomy	2	2		
Variectomy	1	1		
Excision of lipoma of scrotum	1	1		
Amputation of penis	1	1		
Orethrectomy	13	13		
Repair hydrocele	0	19	1 Superficial	
Orethriectomy	~8	~8		
Totals	14~	130	5	3

healed cleanly. Four (5 per cent) presented clinical evidence of wound infection and two of these were superficial. This experience compares quite favorably with that reported by the general surgeons.

Our experiences with cotton in contaminated cases have given quite different results. This group consisted of fifty-four patients whose wounds were either grossly contaminated or drained urine for varying periods (Table II). Thirty-five patients had operations upon the upper urinary tract and nine, or 26 per cent of them extruded one or more pieces of cotton. A number of those in whom nephrectomy was done also had perinephric abscesses. One of these wounds discharged one knot two months after healing had taken place while another extruded one knot eighteen months after the operation. One patient of this group discharged four sutures over a period of four months followed by permanent healing. We cannot consider this an important complication for we feel that the use of cotton in these ten patients afforded quicker wound healing than would have been obtained had catgut been used.

The cotton sinuses which developed in the wounds of those patients subjected to conservative renal surgery were more troublesome. All extruded cotton for at least four months while one persisted in this for eighteen months. In this group was the one granuloma which caused the extrusion of much cotton for eighteen months. Surgical exploration demonstrated a large granulomatous mass which extended down to the peritoneum. It was completely excised and the wound was again closed with cotton sutures without drainage. It healed without infection and no further trouble ensued.

TABLE II. CONTAMINATED WOUNDS

OPERATION	NUMBER	COTTON EXTRUSION
Nephrectomy lumbar approach	10	3 cases— 1 knot at 2 months; 1 knot at 15 months; 4 knots for 4 months
Nephrostomy	4	2 cases for 4 months
Ipyeloplasty	4	1 case for 6 months
Nephrolithotomy	3	1 case for 18 months
Ipyelolithotomy	3	1 granuloma excised
Ureterolithotomy	6	1 case many knots for 6 months
Partial cystectomy	1	Many knots for 6 months
Diverticulectomy	1	
Suprapubic prostatectomy	4	1 case many knots for 6 months
Vesicovaginal fistula	1	Many knots extruded into bladder
Cystostomy	6	1 case few knots for 2 months
Epididymectomy tuberculosis	6	1 case few knots for 4 weeks
Totals	54	14

The sinuses which developed following operations upon the bladder and prostate were also quite bothersome one persisting for six months. The complication following the repair of the vesicovaginal fistula was particularly interesting. Through a Cherney incision the region of the left ureterovesical junction was exposed and the vaginal defect closed with interrupted sutures of No. 40 cotton. The opening in the bladder was closed with interrupted through and through sutures of No. 0 chrome catgut and this was reinforced with Lembert sutures of No. 40 cotton which were placed superficially in the muscle only. The fistula was successfully closed but symptoms of cystitis persisted

Cystoscopy one month after surgery showed the bladder to be normal. Two months later, reexamination demonstrated that two of the cotton sutures had migrated to a submucosal position, they were removed. During the next three months four more cotton sutures were extruded through the mucosa after which vesical irritability ceased. We place no more cotton sutures in the detrusor muscle no matter how far removed from the mucosa. Epididymectomy was done six times for tuberculosis of that organ and of these, one patient extruded four cotton sutures during the next four weeks after which healing took place. These experiences explain why we gave up the use of cotton after one year of trial in cases where urinary drainage occurs. Not only did 25 per cent of them extrude cotton sutures but their incisions were most persistent and quite troublesome to the patient. Only one, however, required surgical intervention for cure.

CONCLUSION

We have been pleased with cotton sutures in the type of case listed in Table I. Late complications from cotton have not been a problem and wound healing has been uniformly satisfactory. These wounds furthermore have been well tested by ambulation of the patient on the day after operation. The low incidence of wound infection is gratifying, and though careful attention was given to technique considerable credit for this must be given to the suture material itself. The use of cotton in contaminated wounds (Table II) was discouraging and we quickly gave it up.

Since this series was closed we have been influenced by the experimental work of Hyde who found that cotton was extruded from contaminated wounds even if the sutures were doubled or placed in a figure of eight manner. In the last three years therefore we have used interrupted single No. 30 cotton in place of the doubled No. 40 figure of eight sutures formerly used. One wonders whether this simple suture might not have decreased the late complications seen in the contaminated wounds.

SUMMARY

- 1 Cotton suture material was used in 196 urologic operations.
- 2 It proved to be a superior suture in wounds which do not drain urine. In this group cotton sinuses and wound infections were rare. We are persisting in its use in these cases.
- 3 Of those wounds which drained urine 26 per cent developed persistent and troublesome sinuses with extrusion of cotton and one of them required surgical excision of a granuloma. Catgut is the suture of choice for these wounds.

REFERENCES

- Bernardi P and Marchi R I. Nuestra experiencia con el Hilo de algodón en cirugía urológica. *Rev argent de urol* 12: 11-115 1943.
Clock P O. The use of American Made Surgical Catgut Suture. *Am J Surg* 58: 292-293 1942.
Derbyshire J. *Ann Surg* 1942.
Hyde T L. *Ann Surg* 1944.
Lorenson S. *Ann Surg* 1944.
of Cotton as Suture Material. *Surg* 16: 407-415 1944.
Use of Cotton for Suture Material.

Table 1. Continued

Experimental and Statistical Study of Suture Material.

LUTK, GYBEC & GIBSI // 48149, 1343

Logue, J B and Walsh W E Cotton Sutures, U S Navy M Bull 38 511 514 1940

Meade W. H. and Ochsner, A. Spool Cotton as a Suture Material, J. A. M. A. 113 2230 2-31 1939

Meade, W. H., and Ochsen, A. The Relative Value of Catgut, Silk, Linen, and Cotton as Suture Material. *Surgey* 7: 485-514, 1940.

M A 117

al Surgerv.

Custer and

1°14 1216.

1241

Taylor, F W Surgical Knots and Sutures, SURGEY 5 498 510 1939

Whipple A O The Choice and Use of Ligatures and Suture Material in the Repair of
Clean Wounds Internat Abstr Surg 69 109 110 1939

Word B. and Brock C. Cotton Suture Material. *Am J Surg* 63 371 3-6 1944

JEJUNAL INTUSSUSCEPTION

UNUSUAL COMPLICATION OF THE USE OF THE MILLER ABBOTT TUBE

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DESPITE the extensive use of the Miller Abbott tube or some one of the modifications thereof serious complications are infrequent. Most of these are related either to the passage of the tube or to pressure of the tube on structures in the upper respiratory tract or esophagus.¹⁻³ Relatively few serious incidents have resulted from passage of the tip of a long tube through the stomach and intestines from the presence of the tube in the intestinal tract or withdrawal of the tube therefrom.⁴⁻⁶

Intussusception producing intestinal obstruction with a Miller Abbott tube in place must be extremely rare, judging by the paucity of such reports. Smith and Van Beuren made the general statement that the intestine has been known to intussuscept itself upon the tube. Harris⁶ cited an experience in which ileum intussuscepted into ileum due to an inflated Miller Abbott tube balloon with death ensuing from an intestinal obstruction and in a personal communication to Harris N. J. Howard described a case requiring operation for intussusception due to a tremendously distended Miller Abbott tube balloon. The only complete case report found in the available literature dealing with this type of accident was made by Warren and Cattell,² one of their cases of stenosis of the intestine terminating fatally with an intussusception and bowel perforation following intestinal intubation. It seems pertinent therefore to record an additional case in which intussusception with intestinal obstruction occurred immediately following the use of a Miller Abbott tube and in which it is believed that intussusception was related to the use of the tube.

CASE REPORT

A 50 year old Negro woman was admitted to the Lankenau Hospital on Sept. 16, 1947, complaining of severe intermittent epigastric and periumbilical pain and repeated vomiting both of twelve hours duration. She had a normal bowel movement the day before admission, but no flatus nor stool had passed since then.

Previous operation included removal of a benign cervical polyp, a supracervical hysterectomy, right salpingo-oophorectomy and an appendectomy on another admission.

Examination showed temperature 37.5° C, pulse 60, respiration 20, blood pressure 140/60. The patient was a well developed and well nourished woman lying in bed belching and vomiting bile stained fluid. The abdomen was diffusely distended but there was neither rigidity nor muscle guarding. Lower abdominal tenderness was more pronounced on the right than the left. No masses were palpable. Peritatic sounds were of normal pitch but hypoactive. Pelvic examination was normal except for the cervical stump which was smooth to inspection but tender on manipulation. Digital examination of the rectum elicited diffuse tenderness. The remainder of the examination was essentially within normal limits.

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roentgenogram of the abdomen did not disclose calculi or distended loops of bowel. An electrocardiographic tracing was normal.

Initial management included continuous gastroduodenal drainage using a Levine tube with a Wangenstein suction apparatus attached, and the administration of parenteral fluids. From Sept. 17 to Sept. 19, 1947, the patient improved, remained afebrile but had copious drainage through the tube. Enemas were returned clear and abdominal distention increased. Therefore, on Sept. 23, 1947 the Levine tube was replaced by a Miller Abbott tube, the balloon of which was weighted with 2 cc of metallic mercury. Difficulty was encountered in passing the tip through the pylorus, but this was achieved on Sept. 26, 1947. After the balloon was injected with 30 cc air, it rapidly advanced to a point in the terminal ileum. Since the tip did not progress further, a thin barium suspension was injected through the tube revealing on a roentgenogram an area of intestinal narrowing. The proximal loop was dilated, but some barium passed the constriction very slowly. On the basis of a near total mechanical obstruction of the ileum operation was performed.

At the first operation, Sept. 30, 1947 (DDD), abdominal exploration revealed the presence of calculi in the gall bladder. Numerous adhesions existed between peritoneum omentum and intestines, and the tip of the Miller Abbott tube was located in the terminal ileum 20 cm proximal to the ileocecum. Compromising the lumen of the bowel immediately distal to the tip of the tube was an obstructing extrinsic band which tightly bound the ileum at this point to a contiguous leaf of mesentery. The band was severed, the entire small intestine was freed of adhesion, and after no further obstruction had been demonstrated the wound was closed.

Twenty-four hours after operation removal of the Miller Abbott tube was begun at the rate of 10 cm per thirty minutes. The balloon which contained 30 cc of air had been deflated and suction on the tube discontinued. The patient experienced crampy abdominal pain and a greater drag was felt on the tube than is usual with its removal. The diet was increased to include soft stools on the second postoperative day and two enemas produced liquid returns containing fecal particles. Anorexia and vomiting on one occasion on the fourth postoperative day were thought to have followed a too rapid increase in the diet. The passage of flatus and two soft brown stools from the eighth to the twelfth postoperative days permitted a sense of security concerning the patency of the intestinal tract. Nevertheless, the patient began to complain of "indigestion" and a sense of abdominal fullness. Anorexia was followed by vomiting slight at first, but increasing within forty-eight hours to large amounts of bilious nonstercoraceous fluid. The nature of the residual gastric contents suggested a high small intestinal obstruction. To confirm this, injection of a thin barium mixture through a Levine tube demonstrated roentgenologically dilatation of stomach and duodenum with complete obstruction in an upper jejunal loop (Fig. 1). The patient having recently had a thorough abdominal exploration the commoner causes of obstruction could reasonably be excluded. However, it was recalled that at laparotomy, elevation of small intestine over the Miller Abbott tube was well demonstrated and in fact a small incipient intussusception was noted. It was suggested in the light of these observations that the obstruction was due at this time to an intussusception in which the

remained. The temperature remained normal limits with appropriate antipyretic therapy the Levine tube in the stomach.

patient was again subjected to a laparotomy.

The second operation was done Sept. 14, 1947 (EWS). At the peritoneal cavity was entered through an upper left rectus muscle splitting incision a dilated loop of small intestine immediately presented. The jejunum was traced from the ligament of Treitz for about 30 cm where a firm obstructing mass an intussusception was met. The intussusception was formed by 15 cm of proximal jejunum which lay within the outer serosal layer of the intussusceptum formed by the distal jejunum. Reduction of the intussusception was accomplished by very gentle traction and pulsion. The bowel wall was edematous but there was no unusual injection nor engorgement save at the neck of the process where moderate hyper-

emus was apparent. With reduction, several small tears were made in the boggy serosa. The mesenteric vessels were not thrombosed. A by passing enteroenterostomy was established, a few pieces of gelatin sponge were placed over the few tiny serosal rents, and the abdomen was closed.

Two days following the second operation the patient was ambulatory and on the third day she had a large spontaneous bowel movement. Gastroduodenal drainage was discontinued on the fourth day and the diet was gradually increased. Subsequent contrast roentgenograms showed slight dilatation of a jejunal loop but free passage of the barium meal to the colon. The patient was discharged on the fifty-fourth hospital day free of symptoms. On a follow-up visit in December, 1948, she was without complaints.



Fig 1—Roentgenogram after barium swallow demonstrating high upper jejunal obstruction.

Comment—One might presume that the Miller Abbott tube was instrumental in producing intussusception in this case. Multiple plications of the intestines on the long tube are usually seen when abdominal surgery is being performed upon intubated patients as noted by McKittrick and Warren¹⁰ and even small transient intussusceptions must be common under these circumstances. The conditions necessary for establishing an intussusception which does not spontaneously reduce are not well defined but one might conjecture that the same physiologic forces are at work which so commonly produce intussusception of the small intestine at the site of a tumor or polyp, the bulky end of the tube being physically analogous to a space-taking bowel lesion. Since the intussusception in this case was not a reverse type it is inferred that the obstruction did not result from withdrawal of the tube. Furthermore obstructive symptoms increased after the first operation which suggests that the

roentgenogram of the abdomen did not disclose calculi or dilated loops of bowel. An electrocardiographic tracing was normal.

Initial management included continuous gastroduodenal drainage using a Levine tube with a Wangensteen suction apparatus attached and the administration of parenteral fluids. From Sept 1 to Sept 19 1947 the patient improved, remained afebrile, but had copious drainage through the tube. Emesis were returned clear and abdominal distention increased. Therefore on Sept 23, 1947 the Levine tube was replaced by a Miller Abbott tube the balloon of which was weighted with 2 cc of metallic mercury. Difficulty was encountered in passing the tip through the pylorus, but this was achieved on Sept 26 1947. After the balloon was injected with 30 cc air it rapidly advanced to a point in the terminal ileum. Since the tip did not progress further, a thin barium suspension was injected through the tube revealing on a roentgenogram an area of intestinal narrowing. The proximal loop was dilated but some barium passed the constriction very slowly. On the basis of a near total mechanical obstruction of the ileum operation was performed.

At the first operation Sept 30 1947 (D.D.D.) abdominal exploration revealed the presence of calculi in the gall bladder. Numerous adhesions existed between peritoneum, omentum and intestines and the tip of the Miller Abbott tube was located in the terminal ileum 20 cm proximal to the cecum. Compressing the lumen of the bowel immediately distal to the tip of the tube was an obstructing cicatricial band which tightly bound the ileum at this point to a contiguous loop of mesentery. The band was severed, the entire small intestine was freed of adhesions, and, after no further obstruction had been demonstrated, the wound was closed.

Twenty-four hours after operation removal of the Miller Abbott tube was begun at the rate of 10 cm per thirty minutes. The balloon which contained 30 cc of air had been deflated and suction on the tube discontinued. The patient experienced cramps, abdominal pain, and a greater drag was felt on the tube than is usual with its removal. The diet was increased to include soft items on the second postoperative day and two emesis produced liquid returns containing fecal particles. Anorexia and vomiting on one occasion on the fourth postoperative day were thought to have followed a too rapid increase in the diet. The passage of flatus and two soft brown stools from the eighth to the twelfth postoperative days furnished a sense of security concerning the patency of the intestinal tract. Nevertheless the patient began to complain of 'indigestion' and a sense of abdominal fullness. Anorexia was followed by vomiting, light at first but increasing within forty-eight hours to large amounts of bile stained nonsterile, corrosive fluid. The nature of the residual gastric contents suggested a high small intestinal obstruction. To confirm this injection of a thin barium mixture through a Levine tube demonstrated roentgenologically dilatation of stomach and duodenum with complete obstruction in an upper jejunal loop.

Fig. 1. The patient having recently had a thorough abdominal exploration the commoner causes of obstruction could reasonably be excluded. However it was recalled that at laparotomy fixation of small intestine over the Miller Abbott tube was well demonstrated and in fact a small intussusception was noted. It was supposed in the light of these observations that the obstruction was due at this time to an intussusception in which the

— intussusception had been compromised. The temperature within normal limits with appropriate the fourteenth postoperative day the end of a Levine tube in the stomach

The second operation was done Sept 14 1948 (F.W.S.). As the peritoneal cavity was entered through an upper left rectus muscle splitting, in situ a dilated loop of small intestine immediately presented. The jejunum was traced from the ligum of Treitz for about 30 cm, where a firm, obstructing mass, an intussusception was met. The intussusception was formed by 19 cm of proximal jejunum which lay within the encasing, liver of the intussusceptum formed by the distal jejunum. Reduction of the intussusception was accomplished by very gentle traction and pulsion. The bowel wall was edematous but there was no unusual injection nor engorgement save at the neck of the process where moderate hyper-

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intussusception developed with the Miller Abbott tube in place rather than from its withdrawal

SUMMARY

1 Serious complications resulting from the Miller Abbott tube are relatively rare

2 An unusual case of jejunal intussusception occurring with the use of the Miller Abbott tube requiring operative intervention and followed by recovery is reported

3 The mechanism for development of such a complication is obscure

REFERENCES

- 1 Iglsauer, S. and Molt, W. F. Severe Injury to the Larynx Resulting From the Indwelling Duodenal Tube. *Ann. Otol. Rhin. & Laryng.* 48: 886 1936
- 2 Wangensteen, O. H., Pea, C. F., Smith, B. A., Jr. and Schwytzer, H. C. Experiences with the Miller Abbott Tube in the Treatment of Acute Intestinal Obstruction. *Surg. gynec. & Obst.* 122: 253-259 1945
- 3 Wangensteen, O. H., Pea, C. F., Smith, B. A., Jr. and Schwytzer, H. C. Acute Mechanical Intestinal Obstruction. *Surg. gynec. & Obst.* 122: 611-622 1946
- 4 Wangensteen, O. H., Pea, C. F., Smith, B. A., Jr. and Schwytzer, H. C. Intestinal Obstruction by the Miller Abbott Tube. *Surg. gynec. & Obst.* 117: 427-436 1943
- 5 Wangensteen, O. H., Pea, C. F., Smith, B. A., Jr. and Schwytzer, H. C. Intestinal Obstruction by the Miller Abbott Tube in Subtotal Colectomy. *Surg. gynec. & Obst.* 117: 345-346 1941

AN ORIGINAL DRAINAGE CUP APPARATUS FOR ILEOSTOMIES AND FISTULAS

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INTRODUCTION

IN THE care of patients with ileostomies, particularly those with profuse watery discharge, the physician and nurse are beset with many problems. Among these may be included the prodigious nursing care necessary because of soilage, irritation, maceration and erosion of the surrounding skin are almost invariable sequelae even after meticulous applications of metallic powders, pastes, resins, etc. designed to protect the skin. Since many of these patients are in a debilitated physical and mental state as a result of the pathologic condition demanding ileostomy, the added insults to the psyche from prolonged hospitalization and mounting expenses contribute incalculable anguish and retard convalescence. Thus it is evident that any apparatus which can afford some measure of relief to these patients is worthy of trial and use. The apparatus to be described was designed for the care of newly created ileostomies until such time that the dejecta become sufficiently formed to allow use of a suitable ileostomy bag. It has performed creditably not only in these cases but also in others (including ceceostomies) with semisolid discharge. It has served satisfactorily in several cases of fistula of the small bowel and of the biliary tract, it should perform well with other types of fistula for example pancreatic ureteral vesical, etc.

DESCRIPTION AND OPERATION OF THE APPARATUS

Suction—An efficient vacuum pump which delivers from three to eight inches (mercury) of negative pressure serves most satisfactorily. Although wall suction is suitable the full negative pressure is not only unnecessary but also undesirable (to be discussed later in paper).

Cup (Fig. 1)—The Lucite cups are provided in three sizes. The smallest is adequate for a small ileostomy whereas the largest is necessary for a double barreled ileostomy or large fistula. In general the intermediate size serves best for all round purposes. In operation the cup is inverted so that the rim is directed toward the skin. A short side arm tube rigidly cemented into an opening just above the rim of the cup provides prompt dependent drainage of the confined discharge. A simple baffle over the roof of the cup is made possible by two discs of Lucite. The lower with a wedge shaped defect is permanently cemented to the roof and gives vent to the beveled intake hole in the roof. The upper disc slightly larger than the lower to prevent sheets, etc. from obstructing the entrance of air, is secured to the lower disc by means of two screws, one of which is permanently fixed and the other, detachable by unfast-

ening the latter, a knurl screw, the upper disc can be rotated on the lower and secured to it in either of two positions. In normal operation the eccentric opening in the upper disc is situated so that it does not communicate with the intake. This arrangement provides the baffle. On the other hand, if one desires to irrigate the cup or to provide exit for an indwelling catheter the upper disc is rotated and fixed so that the eccentric opening overlies the intake.

The cups are transparent light and durable. Since Lucite becomes plastic above 180 F., the cups cannot be sterilized by heat; they can, however, be cleaned with warm soapy water and sterilized with alcohol.



Fig. 1.—Large cup and large rubber base shown separately.

Rubber Base (Fig. 1).—The moulded rubber base which is made of sterilizable rubber sheeting, has the appearance of a wide brimmed hat lacking the roof of the crown. It is provided in three sizes to correspond to the cups. The brim, which is the part cemented to the skin, consists of a round sheet of rubber with a small hole in the center. This opening can be easily trimmed to fit the particular ileostomy, etc. To this brim is attached a short cylindrical crown which fits snugly around the lower half of the cup to prevent leakage. One end of a short rubber tube is attached to the crown above the brim to accommodate the side arm tube of the cup and to complete the watertight jacket; to the other end of this tube is attached the tubing leading to the waste bottle. If the side arm tube of the cup is lightly daubed with lubricant the cup can be easily inserted into (Fig. 2) and enucleated from the rubber base. If while the apparatus is in operation, it is desired to clean the cup, dilate the ileostomy, or apply a protective paste, all that is necessary is to enucleate the cup from the rubber base effect the procedure, and replace the cup.

Cement and Cementing.—Firm adhesion of the rubber base to the skin for four to seven days is possible provided certain precautions are observed. The apposing surfaces of rubber and skin must first be cleansed of oil, water, etc. by naphtha or acetone. With a dry throat stick a uniform layer of cement No.

1 is applied to the skin over the area to be covered by the rubber base. It must be begun at the periphery and continued centripetally in spiral manner to minimize the risk of wetting the cement and imperiling the seal. By pressing the end of a rolled sponge over the stoma during the performance, soiling of the cemented skin can be prevented. A layer of cement No. 2 is then applied to the inferior surface of the rubber brim. The adhesives should be allowed to dry

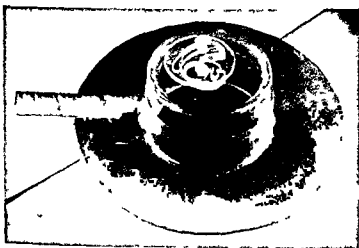


Fig. 1.—Large cup within the rubber base.



Fig. 2.—Small cup in operation. Rubber tubing attached to the side arm tube of the rubber base with the aid of a bent glass tube.

for several minutes before the apparatus is gently but firmly pressed onto the skin with the side arm tube in a dependent position (Fig. 3). If one is dealing with a recently performed ileostomy, aseptic precautions must be observed to prevent infection. The brims, which are large enough to cover freshly sutured wounds and sufficient intact skin for adequate seal, may be trimmed to

the desired size and shape before being cemented. When leakage occurs, the rubber base is slowly and painlessly peeled off the skin with the aid of gauze saturated with naphtha. Before reapplication of the apparatus the residual cement must be removed from the skin by gentle strokes with the dry finger and/or with gauze impregnated with naphtha. After the rubber base is cleaned with water and dried the remaining film of cement should be softened by naphtha and loose islands of the adhesive peeled off, meticulous removal of residual cement is tedious and unnecessary. In reapplying the apparatus one repeats the earlier performance.

NURSING CARE

A protective paste* when applied twice daily in the form of a mound about the ileostomy serves three important functions. (1) It effectively protects the rim of skin around the stoma from erosion. (2) It shelters the cement from undermining attack by the corrosive ferments and prolongs the rubber to skin seal. (3) It shields the projecting ileum from possible wind burn.

Because it is an adsorbent and reportedly inactivates pepsin and trypsin alumina gel is employed periodically to moisten the stoma and clean the cup. If the gel is excessively viscous it is diluted with water. The neck of an aseptic syringe filled with the suspension is introduced through the intake and the ileostomy is coated generously every four hours. Most patients are content to effect their own lavage when the purpose and technique are described to them.

To allow limited ambulation, the suction is discontinued, the side arm tube of the rubber base detached from the tubing leading to the waste bottle, the former clamped and last a rubber stopper inserted into the intake. Thus the patient is provided with a cup type leakproof, ileostomy bag into which the discharge collects. At intervals the patient can empty the cup by reversing the described procedure and can resume ambulation quickly after repeating the earlier performance. If the discharge is especially watery one may prefer to lead the side arm tube into a convenient, ambulatory receptacle. A scull tetus binder has been found helpful in supporting the apparatus particularly when the patient is ambulant.

THEORETICAL CONSIDERATIONS

The baffle serves a fivefold purpose by

- 1 Admitting atmospheric air in replacement of air exhausted from the cup
- 2 Preventing escape of projectile ileal discharge
- 3 Allowing periodic irrigation of the stoma and lavage of the cup
- 4 Allowing limited ambulation

1	Aluminum hydroxid gel powder	50 Gm.
2	Kaolin powder	5 Gm.
3	Starch powder	5 Gm.
4	Anhydrous lanolin	1 Gm.
5	Glycerin	50 Gm.
6	White petrolatum	5 Gm.

Mix the ingredients to make a uniform paste

- c Providing exit for a catheter if indwelling tube drainage of the ileostomy is preferred for the immediate postoperative period. When the catheter loosens it can be removed by gentle traction and the apparatus set into operation by turning on the suction.

When the apparatus is operating, a steady stream of air enters the cup through the baffle, departs through the side arm tube, and carries with it any dejecta or irrigating fluid within the cup. Even with a negative pressure up to one and one-half atmospheres in the suction line, the suction in the cup is negligible for practical purposes, however, to avoid wind burn of the projecting ileum the velocity of the current of air should be kept low by maintaining the effective negative pressure at a level just high enough (three to eight inches of mercury) for prompt removal of the contents.

Though it would seem easy and desirable to effect firm apposition of the apparatus to the skin by means of a constantly maintained gentle negative pressure within the cup, this method is not practical for two reasons: (1) Fluctuations in the line of suction result in loss of anchorage of the cup and in leakage. (2) The slight but inevitable tenting of the stoma and surrounding skin within the confines of the cup gives rise to edema and discomfort; for this reason one should never occlude the intake opening while the apparatus is in operation.

A plea is made that surgeons carefully choose the site of the ileostomy with reference to the umbilicus and anterosuperior iliac spine; exteriorize the stoma at the inferior angle of the wound, suture the latter carefully with small plastic sutures or with fine subcuticular critgut. These precautions greatly influence the immediate and late care of ileostomies and contribute to the comfort and rapid recovery of the patient.

SUMMARY AND CONCLUSIONS

A new and successful apparatus for the care of ileostomies and fistulas is presented.

This simple and durable apparatus is most useful in the early postoperative period following ileostomy, that is, during the phase of profuse discharge of highly irritative digestive fluids; furthermore, it is efficacious in promoting reepithelization of eroded and macerated skin around neglected ileostomies (and rectostomies) by virtue of prompt removal of irritative discharges. The apparatus is also successful in the care of fistulas of the small bowel and biliary tract; it should perform well in the care of pancreatic vesical, and ureteral fistulas.

The tremendous mental and physical lift to the patient and the saving of incalculable time and effort to the nursing staff, not to mention the material economy in laundry and in dressings, are some of the benefits conferred by the use of this apparatus.

For their advice and encouragement the author wishes to thank Drs. Henry Marble, Leland McKittick, Chester Jones, Arthur Allen, Claude Welch, Gordon Donaldson, W. Phillip Giddings, Daniel Ellis, and Arlie Dock, and Mr. John Murphy. He expresses his appreciation to Hood Rubber Co., Watertown, Mass., for their help in developing the apparatus, also to Bovey and Alton Chemical Co., Cambridge, Mass., for their unstinting help in developing new adhesives. The complete sets and replacements are to be manufactured and distributed by Codman and Shurtleff, Inc., 104 Brookline Ave., Boston, Mass.

STARCH SPONGE—A HEMOSTATIC AGENT

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A NUMBER of highly efficient blood coagulants have recently been introduced into medical practice and have been found of great value. The reasons that have impelled me to describe yet another hemostatic agent is its demonstrated effectiveness and low cost.

In 1947 a patent was granted Drs. Rice and MacMasters of the Northern Regional Research Laboratory of the U. S. Department of Agriculture for the manufacture of an absorbable starch sponge. This sponge was to be used in deep or surface wounds, or for any other requirement of internal use. This patent was assigned to the Government of the United States. The dry sponge is capable of absorbing sixteen times its weight of water, and can absorb appreciable amounts of medicaments such as penicillin, gramicidin, sulfapyridine, etc. The sponge dissolves slowly in the body fluids over a period of several days and the dissolved material is absorbed by the body tissues without harmful results. Absorption is of course preceded by enzymatic action.

It seemed to me that in addition to the absorbent qualities mentioned the chemical and physical nature of the starch sponge made it highly probable that the sponge also possessed blood coagulating properties.

PREPARATION

Starch sponge may be prepared from any commercial starch.

To begin with a slurry of starch in water is prepared. This usually contains 5 to 10 per cent of starch by weight. In general, the higher the concentration of starch, the finer the texture of the sponge. At equal concentrations cornstarch makes a firmer sponge than wheat or potato starch. Additions of medicaments that are to be incorporated into the sponge may be made to the slurry or to the paste.

Sponge formation is brought about by slowly freezing the paste. Freezing must be complete throughout the paste before thawing is permitted.

After thawing is completed the sponge is squeezed or pressed to remove free water. If the sponge is to be used wet the material is stored in 70 per cent ethyl alcohol.

The dry sponge is sterilized by cutting it into the desired size and shape and may conveniently be wrapped in heavy paper and tied with a string. These wrapped pieces may then be placed in a container and autoclaved.

The sponge must immediately be dried and this is accomplished by drying under vacuum in the autoclave or by subjecting the sponge to a temperature of 95° C in a drying oven for at least one hour.

The Engineering and Development Division of the Northern Regional Research Laboratory estimated in 1945 that the actual cost of producing the

sponge exclusive of the cost of the starch administration and selling expenses would be 9.48 cents per pound in a plant with a capacity of one ton of starch a day, and 6.67 cents in one with a daily capacity of 5 to 10 tons.

Lee and Lehman² in searching for a substance to replace tale which at times is responsible for the appearance of granulomatous growths, found a corn starch derivative which proved very satisfactory. This starch product replaces tale which is ordinarily used in operating rooms for the preparation of surgeons' rubber gloves. These authors stated: "The fate of this powder (starch) does not offer any great pharmacological problem. Since it is a cornstarch powder it is simply taken up by the peritoneum and metabolized like any ingested starch."

They quoted MacQuiddy (personal communication) who investigated the sensitizing properties of this substance both in human patients and in animals and failed to demonstrate any sensitizing or anaphylactogenic properties.

Lee and Lehman in experiments with the cornstarch product described in their article showed complete absorption from the peritoneum without any demonstrable inflammatory reaction and further stated that it produces no adhesions whatsoever.

MacQuiddy and Tollman³ in an article entitled "An Absorbable Powder to Replace Tale" reported the satisfactory use of a cornstarch derivative treated by physical and chemical means to improve its lubricating value and to prevent elatinization when autoclaved.

Correll Prentice and Wise⁴ reported that starch implants in the muscles of rats could not be identified by gross inspection after the tenth day. The stained specimens revealed fragments of starch through the fiftieth day. No significant tissue reaction to this material was observed but the forty and fifty day specimens revealed an extraordinary cellular infiltration largely of mononuclear phagocytes. The type of phagocyte that usually engulfs lipoids seems to be attracted by this material invading and replacing it.

Although our problem was more concerned with hemostasis than with adhesions nevertheless we performed experiments to determine the action of starch in the presence of hemorrhage and its effect on the peritoneum. The employment of even a markedly efficient hemostatic agent that produces crippling adhesions would indeed only be justified in the direst emergency. Fortunately this did not prove to be the case when starch sponge was used.

We found the sponge to be an excellent hemostatic agent in the rabbit. Experimental animals survived in whom we incised either the large veins of the ear, the femoral vein, or the inferior vena cava. In the case of the auricular or femoral veins the fellow of the opposite side was used as a control. The vena cava experiments were controlled by administering no treatment to some of the control animals and treating others with pressure and gauze packing.

All the untreated animals as expected died within one to two minutes after the vena cava was incised.

When plain gauze was pressed against the opening in the vena cava and left in situ as a pressure pack hemostasis resulted. When these animals were autopsied approximately one month after operation the adhesions encountered

were so dense, and the intestines so compromised that at present with the ready availability of efficient hemostatic agents the practice of employing plain gauze as a packing in cases of hemorrhage should be abolished, except in those instances where no other suitable hemostatic substance can be obtained. Another drawback to the gauze pack is its tendency to disturb the clot and tear tissues on removal so that bleeding commences again.

In every case where the starch was properly applied to any of the venous structures mentioned previously, including the vena cava, the animal survived.

We found that the best method of obtaining hemostasis with the starch sponge was to moisten one end of the dry starch bar with sterile water or saline solution, and to cover the opening in the vein with this moistened end simultaneously creating pressure by bearing down on the dry end of the bar. When all bleeding ceased, usually a matter of one to two minutes the whole or part of the bar was left in situ.

Large pieces of starch were left in the peritoneal cavity of some animals so that the effect of massive pieces on starch sponge could be studied.

Taking into consideration the fact that the vena cava is located in the retroperitoneal space the cellular tissue of which is almost embryonal in its reaction to stimuli such as irritants, foreign bodies, etc., the adhesions we found at autopsy usually performed three to four weeks after operation were surprisingly moderate.

To study the reaction of the general peritoneal cavity to the sponge rather than that in the retroperitoneal space we introduced large pieces of dry and wet sponge among the intestinal coils without opening any large vessel. At autopsy gross inspection in the majority of these animals revealed none or minimal adhesions. One animal however showed a walled-off sac attached to one of the intestinal coils. Another animal showed a small granulomatous lesion in the lower angle of the peritoneal incision. It should be taken into account that much more starch was used in these animals than would ever be found necessary to employ in a human being weighing many times more than the experimental animal. All of these animals survived, appeared healthy and had gained in weight in the three to five week interval between operation and autopsy.

Frantz² in discussing Oxyel stated that cysts are sometimes found in serous cavities where a relatively large mass of material is surrounded by serous membranes. Such cysts usually resorb.

CLINICAL CASES AND SUMMARY

We have to date used the starch sponge in fifty-three gynecologic and obstetric patients to control bleeding. In addition the Mohels (ritual circumcisers) have used the cornstarch powder as prepared by the United States Department of Agriculture in approximately one hundred cases.

Intraperitoneal applications were made in twenty patients, in the course of operations such as hysterectomy, myomectomy, and in one case of a ruptured corpus luteum cyst of pregnancy. It was employed in nine cases of cesarean section; in seven of these patients it was used to control bleeding on the uterine

surface, and in two patients the sponge was introduced into the uterine cavity via the uterine incision.

In a patient who had several hemorrhages due to retained secundines following full term pregnancy several pieces of starch were introduced into the uterine cavity. This was done only after profuse bleeding continued despite the fact that the curette failed to locate any additional products of conception. Immediately after the introduction of the starch bleeding ceased and no cervical or vaginal packing was employed.

An intrauterine application of gauze bandage impregnated with starch sponge was performed on the second post partum day of a patient who suffered a severe post partum hemorrhage despite the fact that the uterus and vagina were tightly packed with gauze. This patient had a splenectomy at the age of 12 years because of thrombocytopenic purpura. On the basis of this history the obstetrician had taken the precaution of giving her transfusions before and after delivery and tightly packing the uterus with plain gauze. Despite these precautionary measures a severe hemorrhage ensued and she exhibited many of the signs and symptoms of impending death. The gauze pack was removed and a starch sponge pack introduced. The bleeding ceased almost immediately and she was discharged from the hospital in good condition on the eleventh post partum day.

We were fortunate in having another patient present herself in whom a control observation was possible. This case concerns a woman of 70 years. She had a prolapse of the uterus and had worn a pessary for many years. Her doctor removed the pessary because of pressure symptoms and after several weeks an attempt was made to reinsert it. Great difficulty was encountered and the attempt at reinsertion was abandoned. However the vaginal walls had sustained multiple lacerations and hemorrhage ensued. Several vaginal packings of plain gauze were ineffectual in controlling the bleeding. She was admitted to the hospital where the gauze pack was removed and starch sponges substituted. The sponges were maintained in position by placing a small amount of gauze in the vaginal orifice external to the outermost starch sponge bar. The bleeding was promptly controlled.

Starch sponge in powder form or gauze impregnated with the starch sponge powder was used eleven times after cervical cauterization, eighteen times in the course of vaginal plastic operations, twice in the rectum after removal of polypi and cauterization of hemorrhoids and once in the thigh after the resection of fused lata for purposes of transplantation.

The Mohels stated that they have used it with satisfaction in approximately one hundred ritual circumcisions.

There was no mortality in this series. There was one morbidity that might have possibly been due to the intrauterine introduction of starch sponge. This occurred in a patient who had retained secundines and continued to bleed after curettage. The uterus was packed with starch sponge. A few hours after operation her temperature rose to 105° F. One cannot be certain that the starch sponge was the responsible agent for she received a blood infusion and the possibility of intrauterine infection could not be excluded. Both of the latter factors

are competent producing causes for the reaction that this patient exhibited and either might just as well have been the etiologic mechanism. The patient left the hospital in good condition on the fourth postoperative day.

CONCLUSION

Starch sponge is an efficient hemostatic agent. Its effects appear to be purely local and its hemostatic action is probably due to its gel formation. It can absorb many times its weight in blood. This causes the sponge to swell and to exert pressure, thus forming a mechanical obstruction to the flow of blood.

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August 1947

APPENDIX

Since this article was submitted starch either in the form of the sponge or the powder or the impregnated gauze bandage has been used in forty one additional patients.

Case Reports

PRIMARY SPLENIC SARCOMA

REPORT OF CASE

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DENVER, COLO.

PRIMARY malignancies of the spleen are rare. Hausmann and Gaarde¹ collected 178 cases in 1940 nine of which they added from the Mayo Clinic. Mentzer and Jones² added two cases from the Cleveland Clinic in January 1948, ten cases having appeared in the meantime bringing the total to 190. These two cases constituted the only primary malignant tumors seen in that clinic in two decades and the one operative case was the only splenectomy for primary splenic malignant disease among 20,000 major surgical procedures.

CASE REPORT

A 6-year old mother of three children complained for three months of pain in the left side of the body including arm, shoulder, chest and upper abdomen. On self medication with vitamin the arm and shoulder pain became better but the abdominal pain became worse. Flatulence and occasional vomiting occurred and she noted that deep inspiration and eating accentuated the pain in the left upper abdomen. She had lost twenty-seven pounds in weight, the appetite became poor, there were no bowel changes and the vomitus never contained blood. She had had bronchial asthma for thirty-seven years starting with what he guessed was tuberculosis. There had been no attacks for years until two weeks before admission to the hospital on Dec. 10, 1947.

Examination revealed a somewhat obese woman of short stature. There were râles at the left base, the left diaphragm was elevated about two inches and a firm moderately fixed mass was palpable in the pleuro area. It extended about 2 to 3 cm. below the costal margin and was about 4 to 5 cm. wide. There was only one palpable lymph node deep in the left axilla.

Tentative diagnosis of malignancy involving the left diaphragm was made at the first visit and she was referred for x-ray study. The chest revealed several healed tuberculous lesions. The barium enema was negative. The stomach was reported to show a lesion at the fundus but the roentgenologist suggested a gastroscopy since his findings were somewhat equivocal. The gastroscopist disclosed no lesion of the stomach but since the area of the upper tumor lay where the gastroscopist could not directly reveal it another gastric x-ray was recommended. This more definitely suggested a gastric lesion. The gastric analysis was normal. Another roentgenologist decided the lesion was extragastric. Intravenous pyelograms revealed normal kidneys. In view of the palpable mass in the splenic area, lack of hematocrit, normal gastric analysis and the other findings enumerated a diagnosis of malignant tumor of the spleen was agreed upon.

On entrance to the hospital the patient had a temperature of 101° F. and many râles in the chest. The red cells in the blood varied from 3,670 to 5,960 million per cubic millimeter during the preoperative period. The leucocytes ranged from 11,500 to 17,500 per cubic millimeter of blood and the differential smear ranged between 78 and 91 per cent neutrophils, 9 and 12 per cent lymphocytes, 1 and 3 per cent monocytes and an occasional undifferentiated blast cell. A dramatic shift to the left developed preoperatively with the presence of 14 per cent juvenile forms being observed at one time. A lymphoma as the source of the occur-

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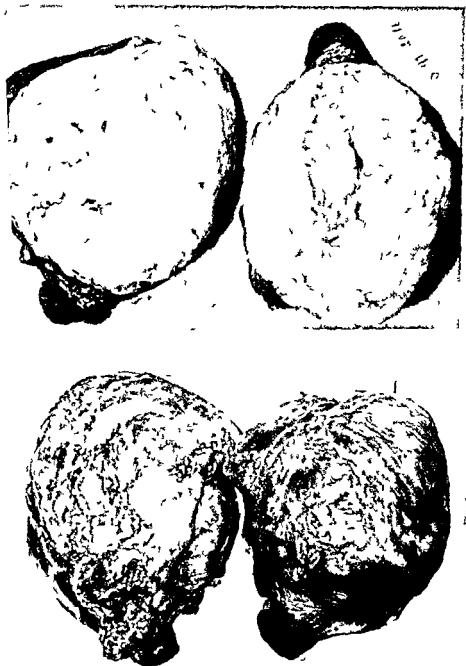


Fig. 1

Fig. 2

Fig. 1.—Sealed specimen of *Peridroma salicis* (left) and *Peridroma salicis* (right) showing the dorsal view of the head. The right half is larger than the left half.
 Fig. 2.—Cut surface of the head of *Peridroma salicis* (left) and *Peridroma salicis* (right) showing the ventral view of the head.

small blast cell visualized in the peripheral blood was considered as probable on clinical correlation. The patient felt worse, and dated the increased malaise from the time of the gastroscopy. The operation was postponed from day to day until two weeks had elapsed. During this period, three chest x-ray pictures showed no change in the original findings, and in spite of intensive treatment the fever was not reduced.

Under intratracheal anesthesia, the patient was placed upon the right side in preparation for the combined abdominothoracic incision as described by Garlock. The abdomen was opened by a high incision lateral to the rectus muscle. The stomach was free of disease; there were no palpable metastases and the spleen was enlarged and densely adherent to the diaphragm. It was felt that abscess of the spleen could not be ruled out and it was decided to remove the spleen. The incision was extended across the costal margin and through the

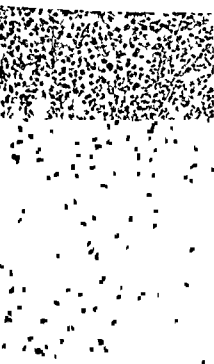


Fig. 3

Fig. 3—Undifferentiated large reticulum cells bordering on an area of necrosis (hematoxylin and eosin stain).

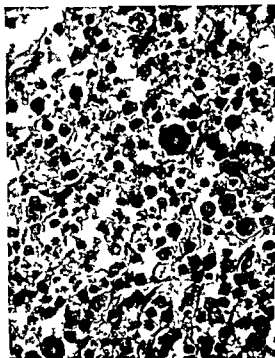


Fig. 4

Fig. 4—Reed-Sternberg type of giant cells surrounded by the more characteristic undifferentiated reticulum cells (hematoxylin and eosin stain).

with interspace posteriorly. The lung was adherent to the diaphragm and was freed easily. The diaphragm was replaced by gravity tissue and a portion was removed from the superior surface for frozen section. It revealed anaplastic malignant tissue. Section of the left half of the diaphragm and replacement by ox fat came out and rejected. The spleen was separated from the diaphragm and removed. The phrenic nerve was crushed and the wound closed with chromic catgut encircling the ribs and black silk closure with no drain.

Recovery was largely uneventful although the fever persisted. The wound healed without incident. Fluid to the amount of 500 cc was removed from the left side of the chest two weeks after operation and showed no leucocyte or organisms on smear and no growth on culture. X-ray treatment was started one week after operation but was not tolerated well and was given up. The patient left the hospital sixteen days after operation and died at home 16 days later. An autopsy was not done.

The spleen was enlarged weighed 870 Gm. and measured 16 by 13 by 12 cm. Approximately three fourths of the spleen was replaced by a 12 cm in diameter spherical white, relatively firm tumor which presented prominent roughened adhesions on its diaphragmatic surface. The usual reddish rubbery type of spleen was present as a rim on two sides.

On section by a yellowish brown tumor while three of the larger lymph glands presented a light pink, meaty cut surface. Section of spleen revealed a mesenchymatous type of tumor whose central portion was light yellow and of a soft putty nature. Tumor was not clearly demarcated and the detectable spleen peripherally presented redder softer irregular poorly defined points of invasion.



Fig. 1.—Wilder's reticulum stain showing abundant reticulum.

Microscopic examination revealed the greater portion of the tumor to be sarcomatous. Tumor cells were undifferentiated relatively large (two to three times the size of a lymphocyte) and revealed no definite architectural pattern but an unorganized diffuse arrangement in broad sheets. Tumor cells presented large hyperchromatic nuclei, prominent enlarged nucleoli, many mitoses and an abundant foamy type of cytoplasm. Tumor cells for the most part were observed as relatively uniform but in localized areas there were prominent multinucleated giant cells which at times presented horseshoe-shaped hyperchromatic nuclei and light eosinophilic cytoplasm. Wilder's reticulum stain revealed prominent interovenous reticulum throughout the greater portion of the tumor.

Sections of the pancreas, fatty fibroconnective tissue of the hilum and a portion of the diaphragm revealed direct extension of the described tumor. One lymph gland was found to be subtotally replaced with tumor essentially similar to that of the spleen while three lymph

glands revealed a non specific hyperplasia with no tumor involvement. This lesion histologically was classified as reticulum cell lymphosarcoma on the basis of the large and uniform undifferentiated cells and the abundant reticulum demonstrated by Wilder's reticulum stain. The large multinucleated giant cells which at times resembled Reed Sternberg cell suggested Hodgkin's sarcoma as a possible diagnosis. Clinicopathologic correlation indicated this tumor as a primary lesion of the spleen.

COMMENT

It seems probable that this disease produces few if any symptoms until neighboring structures are involved whereupon the prognosis becomes almost hopeless. After a growth of this sort involves adjacent structures removal merely hastens the end. If it can be attacked before such direct extension has occurred the prognosis seems to be remarkably good. The combined abdominothoracic incision is excellent permits exploration before the chest is opened and should have a wide range of usefulness. Whether a rib is removed or the intercostal incision is used would seem to depend on the prejudices of the operator.

REFERENCES

1. Haumann P F and Caarde, F W. Malignant Neoplasms of Spleen. Review of Literature and Report of Case of Primary Lymphosarcoma (Reticulum Cell Type). *Cancer* 14: 246-253 1943.
2. Mentzner W R T and Jones, T F. Primary Splenic Sarcoma of Hodgkin's Type. *Cleveland Clin Quart* 15: 1823 1948.
3. Carlock J H. Combined Abdomino Thoracic Approach for Carcinoma of Cardia and Lower Esophagus, *Surg Gynec & Obst* 83: 57-61 1946.

The spleen was enlarged, weighed 870 Gm. and measured 16 by 13 by 12 cm. Approximately three fourths of the spleen was replaced by a 12 cm. in diameter, spherical white relatively firm tumor which presented prominent roughened alveolar nodules on its diaphragmatic surface. The usual reddish rubbery type of spleen was present as a rim on two sides. The hilum included a portion of the pancreas which was grossly recognized and this measured 1.5 to 2 cm. in diameter. The fatty fibroconnective tissue attached to the hilar vessels included detectable lymph glands ranging between 5 and 15 mm. in diameter. One of these appeared to be subtotally replaced by a yellowish brown tumor while three of the larger lymph glands presented a light pink, meaty cut surface. Sections of spleen revealed a semicartilaginous type of tumor whose central portion was light yellow and of a soft putty nature. Tumor was not clearly demarcated and the detectable spleen peripherally presented redder softer irregular poorly defined points of invasion.



Fig. —Wilder's reticulum stain showing abundant reticulum

Microscopic examination revealed the greater portion of the tumor tissue to be necrotic. Tumor cells were undifferentiated, relatively large (two to three times the size of a lymphocyte), and revealed no definite architectural pattern but an unorganized diffuse arrangement in broad sheets. Tumor cells presented large hyperchromatic nuclei, prominent enlarged nucleoli, many mitoses, and an abundant, misty type of cytoplasm. Tumor cells for the most part, were observed as relatively uniform but in localized areas there were prominent multinucleated giant cells which at times presented horseshoe shaped hyperchromatic nuclei and light eosinophilic cytoplasm. Wilder's reticulum stain revealed prominent interwoven reticulum throughout the greater portion of the tumor.

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REFERENCES

1. Haumann P. F. and Gaarde F. W. Malignant Neoplasms of Spleen, Review of Literature and Report of Case of Primary Lymphosarcoma (Reticulum Cell Type). *Surgery* 14: 246-255, 1943.
2. Mentzner W. R. T. and Jones T. E. Primary Splenic Sarcoma of Hodgkin's Type. *Cleveland Clin Quart* 15: 18-23, 1943.
3. Garlock J. H. Combined Abdomino-Thoracic Approach for Carcinoma of Cardia and Lower Esophagus. *Surg Gynec & Obst* 83: 73-74, 1946.

Surgical Technique

THYMECTOMY FOR MYASTHENIA GRAVIS

SURGICAL TECHNIQUE

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ALTHOUGH little is known about the thymus gland and its functions a considerable body of evidence has accumulated to indicate that there is a definite relationship between this gland and the disease myasthenia gravis. The first surgical attempts to treat patients with myasthenia gravis by removal of the thymus gland were made by Sauerbruch.¹ These attempts were made before neostigmine had been developed for the medical treatment of the disease and before thoracic surgery had advanced to its present status.

Blalock and associates² were the first to perform thymectomy for myasthenia gravis with apparent success. Since their report, a considerable number of thymectomies have been reported. There has been some variation in the results obtained from operation but most surgeons have agreed that thymectomy does not provide a surgical cure of myasthenia gravis in all cases. Some patients have apparently benefited greatly, but in others the disease has apparently not been affected. It has been impossible from experience thus far to determine which patients with myasthenia will benefit from operation and which will be unaffected. It has likewise been impossible to establish any relationship between the pathologic changes found in the thymus gland at operation and the severity of the myasthenia gravis or to predict on the basis of observed pathologic features the benefit that might be expected from operation. Although we cannot predict the benefit to be gained by thymectomy in the treatment of myasthenia gravis in any individual case some patients have shown improvement in the severity of myasthenia after thymectomy and in a few cases complete remission of the disease has occurred. In no case has myasthenia gravis become worse after operation.

It has been our policy to suggest thymectomy in the treatment of patients with moderately severe myasthenia gravis and patients whose disease appears to be progressive. We have not urged operation in cases of mild myasthenia gravis which is well controlled by neostigmine therapy and we feel strongly that operation should be delayed in patients with very severe manifestations of the disease until it is in remission since the severely myasthenic patient is a very poor surgical risk.

PREOPERATIVE CARE

Preoperative preparation is extremely important. The patient should be in the hospital for a few days before operation if possible. This permits complete rest and a period of observation so that the requirements of the patient

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for neostigmine can be determined accurately. Myasthenic patients are very susceptible to respiratory infections and should be fully protected from exposure. A preoperative course of penicillin may be indicated. Most female patients with myasthenia gravis note an exacerbation of the disease just before the menstrual period. Operation should be deferred until menstruation has ceased in these patients.

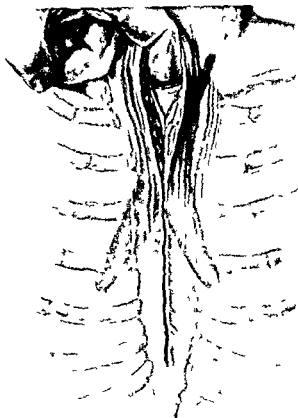


Fig. 1.—The incision extends from the manubrial notch to the xiphoid process. The soft tissues are pulled away from the anterior wall of the sternum and the internal chest is exposed.

Many myasthenic patients are thin, weak, and undernourished because of their difficulty in chewing and swallowing. Every effort, even including feeding by tube, should be made during the preoperative period to restore the patient's nutritional status. Oral neostigmine therapy, as required by the individual patient, should be continued up to the time of operation. Heavy preoperative sedation is to be avoided. We prefer to avoid the use of barbiturates for preoperative sedation since myasthenic patients are depressed excessively by such drugs. Just before operation the patient should be given 10 to 15 mg. of neostigmine methylsulfate $\frac{1}{6}$ to $\frac{1}{8}$ gr. (0.008 to 0.01 Gm.) of morphine and

$\frac{1}{10}$ gr (0.00043 Gm) of atropine subcutaneously. The anesthetic of choice is nitrous oxide, oxygen and ether administered through an intratracheal tube. Sodium pentothal and curare are definitely to be avoided.

Branch of
internal
mammary
artery

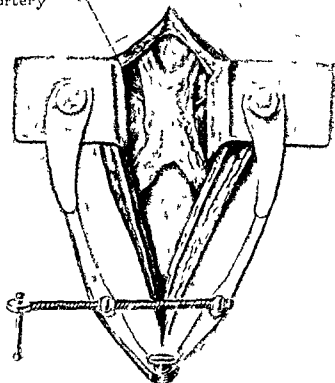


Fig. 9.—The split sternum is separated exposing the thymus.

OPERATIVE TECHNIQUE

A variety of surgical approaches has been used in operations upon the thymus gland. Partial thymectomy has been performed from a cervical incision. Since the thymus gland extends well down over the pericardium this approach does not permit resection of more than a small portion of the thymus and is entirely inadequate. In the case of large thymic tumors which occur not infrequently in instances of myasthenia gravis it may not be possible to obtain adequate exposure through a sternum splitting incision and in such cases a posterolateral transpleural approach to the anterior mediastinum may

be necessary. In some cases this approach will not permit complete removal of the portion of the thymus gland which extends up into the neck in the region of the inferior poles of the thyroid gland.

The most satisfactory approach for complete removal of the thymus gland in patients with myasthenia gravis is the sternum splitting incision. The skin is incised vertically over the sternum from the manubrial notch to the xiphoid process. The dense layer of pretracheal fascia attached to the posterosuperior edge of the manubrium is cut and a finger is inserted behind the manubrium.

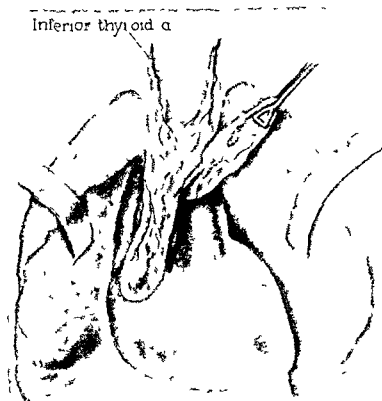


Fig. 1.—The lower lobe of the thymus gland extends down to the pericardium; the upper lobes extend up into the neck.

pushing the soft tissues away from the base (Fig. 1). A Heubach sternal chisel is then inserted and the manubrium and sternum are split in the midline to the xiphoid process. The manubrium is a rather dense bony structure particularly in adults but the sternum splits quite easily. There may be considerable oozing of blood from the sternal marrow. A self-retaining retractor is inserted and the split sternum is spread apart exposing the anterior mediastinum (Fig. 2).

At first glance the thymus gland may not be noted in the loose areolar and fatty tissue of the anterior mediastinum but a little dissection will disclose it. It is pinkish gray in color, has a fine granular appearing surface, and has a

very thin but definite capsule in most instances. It is a bilobed gland joined in the center just over the left innominate vein, with thin extensions going up toward the lower poles of the thyroid in the lower cervical region and rather broad, flat lower lobes spread out over the pericardium. The gland receives its blood supply from the branches of the inferior thyroid artery which go to the upper poles, and from branches of the internal mammary artery which enter the gland laterally at about the level of the isthmus that joins the two sides. The venous drainage from the gland is through one or occasionally two vessels passing directly from the posterior wall of the isthmus of the gland into the left innominate vein. These blood vessels are remarkably constant in their location and number.

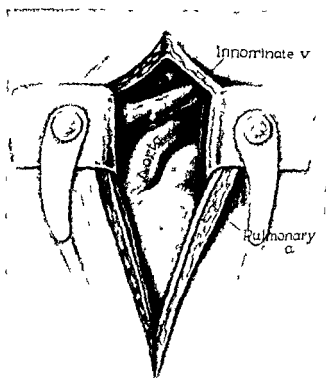


Fig 4.—After removal of the thymus gland the great vessels in the superior mediastinum are exposed.

The thymus gland is likely to be quite adherent to the pleura laterally and it is very easy to open the pleura inadvertently during the dissection. The gland extends posteriorly to the level of the phrenic nerves and extends down over the pericardium. Since the gland is quite friable it must be handled gently (Fig 3). After the gland has been completely excised the arch of the aorta and its branches the pulmonary artery the left innominate vein and the anterior pericardium are completely exposed (Fig 4).

We formerly used encircling steel wire sutures around the sternum for its approximation in closure. There was always some danger of injuring the internal mammary artery as these sutures were inserted and we now use only interrupted catgut or silk sutures in the fascia and periosteum on the anterior surface of the sternum (Fig 5). The subcutaneous tissues and skin are approximated with interrupted sutures. No drains are used. If the pleura has been opened inadvertently during the operation no attempt to close the opening is made but all air is aspirated from the pleural space by means of a catheter, and the anesthetist maintains expansion of the lung with positive pressure as the wound is closed.

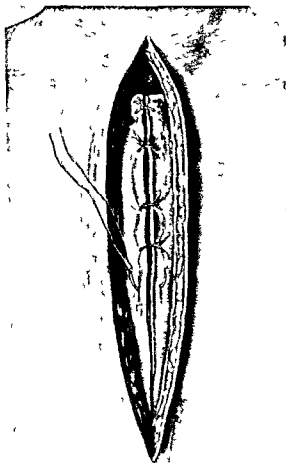


Fig 5—Sternum is approximated with interrupted stitches in the anterior fascia.

It should be mentioned that although the thymus gland usually lies anterior to the innominate vein in two cases in our experience the gland lay entirely behind the vein and in another the right lobe lay anterior to the vein and the left lobe posterior to the vein.

Occasionally during thymectomy performed on patients with myasthenia gravis, some weakness of respiratory effort may be noted. Neostigmine methyl sulfate in 10 mg doses should be available in the operating room and a dose should be administered subcutaneously at once under these circumstances. Neostigmine causes some increase in oral and tracheobronchial secretions. The pharynx and tracheobronchial trees should be aspirated as necessary during the operative procedure and particularly at the end of the operation. Occasionally postoperative bronchoscopy will be necessary to remove retained secretions.

POSTOPERATIVE CARE

Postoperatively the patient should be placed in an oxygen tent for twelve to twenty-four hours in most instances. An respirating device should be readily available to remove secretions from the mouth and pharynx until the patient has recovered from anesthesia. A Drinker type respirator should be kept in readiness preferably in the patient's room and the patient should be placed in the respirator if there is any evidence of weak or inadequate respiratory function in spite of neostigmine therapy. A respirator has been lifesaving in several of our cases. Neostigmine methylsulfate in 10 mg doses, should be given subcutaneously every two to three hours postoperatively, and this dose may be doubled or given every hour if the patient's condition is not satisfactory. Theoretically it may be possible to give a patient too much neostigmine. From a practical standpoint it is much better to err on the side of giving more neostigmine than is necessary to the postoperative patient with myasthenia gravis than it is to err on the side of giving too little. Oral administration of neostigmine bromide in doses of 15 mg should not be resumed postoperatively until the patient is able to swallow and then the dosage should be adjusted to the patient's requirements which are usually met by about the same program that the patient had found to be adequate preoperatively.

A sudden and dramatic relief of the manifestations of myasthenia gravis is not to be expected. Some of our best results have occurred in patients who were not able to reduce their neostigmine requirements for several weeks or months after operation. Increased salivation and abdominal cramping incident to the large doses of neostigmine required in some patients postoperatively can be minimized by the administration of atropine sulfate in doses of $\frac{1}{150}$ gr (0.00043 gm). Heavy postoperative sedation of any kind is to be avoided except in patients who become so nervous and exhausted that it is necessary to place them in the Drinker respirator for a time. Small doses of codeine or morphine should be used to control pain. Large quantities of pain relieving drugs are not necessary since patients with this disease seem to have relatively little postoperative pain. The patients are allowed out of bed in forty-eight hours and are usually dismissed from the hospital within one week.

RESULTS OF OPERATION IN EIGHTY-FIVE CASES

Our experience with operations on the thymus gland in patients with myasthenia gravis is based on eighty-five cases. Thirty-one of the patients had tumors of the thymus; fifty-four did not have tumors. The presence of a thymic

tumor had been demonstrated by radiologic examination preoperatively in thirty instances. In only one instance was a tumor of the thymus suggested by radiologic examination and not found on surgical exploration. The high incidence of thymic tumors in this group of cases does not represent the true incidence of thymic tumors in myasthenia gravis, the true incidence is about 1 per cent. This high figure results from our policy of urging all patients with thymic tumors to have an operation regardless of the status of the myasthenia gravis because of the potential danger of the tumor.

Thymectomy was often offered to patients without evidence of thymic tumor if the myasthenia gravis was moderately severe or progressive, but was never urged under any circumstances. Our rather conservative surgical attitude is indicated by the fact that in a period of seven and one half years 75 patients were operated upon while 142 other patients with myasthenia gravis observed in the same period were not operated upon.

In our series of eighty five operations on patients with myasthenia gravis there were seven deaths. Five deaths occurred in patients with tumors and two in those without thymic tumors. The deaths, with one exception, were due to complications of myasthenia gravis rather than related to the operative procedure itself. There were no wound complications. Unless complications related to the myasthenia gravis developed patients were able to leave the hospital within one week or ten days after operation in all cases.

Myasthenia gravis is a disease that varies greatly in severity and is subject to remission and exacerbation without apparent cause. This fact has made an accurate evaluation of the effect of thymectomy on the course of the disease very difficult. However we have attempted to make a careful follow up study of 217 patients with myasthenia gravis by comparing a group of 75 patients treated by thymectomy with a group of 142 patients treated by medical measures observed over the same period of time. It had been our clinical impression that the patients who had thymectomy had shown some improvement over those not operated upon. However our follow up study has failed to demonstrate any significant benefit from thymectomy that can be attributed to the operation. Over the period of observation ranging from one to seven and one half years the course of the disease was essentially the same in the patients who did not undergo operation as in those who did. While it must be admitted that thymectomy apparently does not benefit the myasthenic patient it should also be noted that there was no instance in which the symptoms of myasthenia gravis could be said to have been made worse.

CONCLUSIONS

As a result of our experience we have come to the following conclusions regarding the thymus gland and myasthenia gravis.

1. There is some connection between the thymus gland and myasthenia gravis. It cannot be pure coincidence that tumors of the thymus occur in 15 per cent of all cases of myasthenia gravis. The exact nature of the relationship between the thymus and myasthenia gravis is unknown.

2 All patients with myasthenia gravis should be studied thoroughly for evidence of thymic tumors. Simple posteroanterior roentgenograms do not give an adequate basis for diagnosis since the tumor is often hidden behind the sternum. Roentgenoscopic examination as well as lateral and oblique films will be necessary to demonstrate many thymic tumors.

3 Thymectomy should be advised in all instances of thymic tumor unless the condition of the patient makes the risk of operation prohibitive. Such a tumor may be well encapsulated and apparently benign. In other instances the tumor may show malignant characteristics with invasion of surrounding tissues. In a few instances the tumor has proved to be inoperable due to invasion of the pleura and lung, pericardium and great vessels.

4 Thymectomy may be suggested in carefully selected cases of myasthenia gravis if the disease is moderately severe or progressive. It should not be advised if the disease is very mild or very severe because the patient with mild disease will probably not be benefited and the patient with very severe disease is a very poor surgical risk. The results of thymectomy in the treatment of myasthenia gravis are unpredictable. We have not been able to show statistically that patients with myasthenia who had had thymectomy have benefited materially from operation when compared with a group treated by medical means.

REFERENCES

- 1 Sauerbruch. Quoted by Blalock, Mason, Morgan and Riven.²
- 2 Blalock, Alfred, Mason, M. F., Morgan, H. J. and Riven, S. S. Myasthenia Gravis and Tumors of the Thymic Region. *Ann. Surg.* 110: 544, 1940, 1949.

Editorial

Further Specialization

WITHIN the past several months two major conferences have been held to discuss a specific pathologic process—one, in New York, the First Annual Scientific Meeting of the Gerontological Society and the other in Memphis the National Cancer Conference. Those who attended both meetings may have been struck by the similarity of approach at these meetings. Because the study of both the aging process and cancer concerns many diverse groups there were present biologists, internists, surgeons, the medical and surgical specialists, as well as the social scientists to contribute to the discussions.

In spite of the fact that we now have the oncologist and may soon have the gerontologist it must be apparent that significant advances in the knowledge of both malignant disease and the aging process will require the cooperation of many disciplines. There is a grave danger in further multiplying the medical and surgical specialties without giving sound thought to what may be sacrificed for that which is gained.

One is reminded of Harvey Cushing's statement on this subject. The specialties are justified solely by their productiveness. It might be wise for each of them occasionally to come back to the mother tree for suckling.

It is seriously questioned whether oncology or gerontology should be treated as specialties to be organized as isolated subjects in medical teaching or in residency training except at a graduate level above the mother tree. Specialization in these fields should originate from the parent specialty, but specialty boards in either field are unnecessary.

Medical education must be sufficiently broad to train internists with a special interest in the medical problems of old age as well as surgeons with a special interest in the surgical problems of old age. The same is true for oncology. In each instance the special interest from the standpoint of clinical practice should be engrafted on thorough training in internal medicine or general surgery.

—I S. Raizen

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

MALIGNANT NEOPLASMS OF THE THYROID

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IT IS well known that in a considerable proportion of cancers the ultimate malignant state is an attribute acquired only after a variable interval of time in a well recognized progression from a benign precursor. In attempting to reduce the number of deaths from cancer of any organ a most important consideration is the early recognition and eradication of precancerous lesions where such are known to exist.

Many authors have recently stressed the high incidence of malignancy in adenomatous goiter. Indeed so frequent is the relationship of thyroid adenoma to malignancy that the attitude of regarding all adenomatous thyroid glands as having significant malignant potentialities is constantly gaining adherents. Data from the University of Michigan Hospital support this attitude and the corollary that (unless strong contraindications exist) thyroidectomy should be recommended whenever the diagnosis of adenomatous goiter is made regardless of the presence or absence of hyperthyroidism.

This report makes available the material from the departments of pathology and surgery together with a selective review of the literature pertaining to thyroid malignancy.

INCIDENCE

During the ten year period from June 1935 through July 1945 thyroidectomy was performed upon 1326 patients in this hospital. Cancer was found in 61 instances, or an incidence of 4.6 per cent among all surgically treated goiters. In the series recently reported by Horn and associates¹¹ the incidence was 3.0 per cent of all surgically treated goiters (62 carcinomas in 2079 surgical goiters). Ward¹² also reported an incidence of 3.0 per cent (168 cases of malignancy in 5439 surgical goiters). Foss¹³ averaged the reports of 11 authors and obtained a figure of 2.37 per cent as the incidence of malignancy in surgically treated goiters.

In the present series it was felt worth while to study the cases in a manner that would correlate the possibility of malignancy to the type of goiter found on physical examination. Accordingly three groups were selected: the first consisting of patients having a palpable nodular or adenomatous goiter on physical examination (and this group was further subdivided into those having multiple nodules and those having a single nodule); the second group consisting of patients having a palpable diffuse goiter without clinically discernible nodules; and the third group being comprised of patients presenting no palpable thyroid enlargement. Table I summarizes these data.

TABLE I CLINICAL GROUPING BASED ON TYPE OF GOITER PRESENT

	TOTAL NUMBER OF CASES		TOTAL NUMBER MALIGNANT		PER CENT MALIGNANT	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
Group I Palpable nodular goiter	63	113	45	13	65	91
(a) Multinodular	56	115	34	11	60	956
(b) Single nodule	151	28	11	2	84	714
Group II Palpable diffuse goiter	315	126	—	—	06	—
Group III No palpable goiter present	22	24	1	—	45	—

It may be seen from these figures that the incidence of malignancy in individuals with adenomatous goiters (combining both sexes and with multiple adenomas as well as single adenomas) in this series is 6.94 per cent. In Horn's series the incidence was 5.5 per cent and in Ward's series³¹⁻³³ 4.8 per cent. Cole and associates¹⁰ reported an incidence of 7.2 per cent in nodular goiters and called attention to the fact that the incidence varies throughout the country, suggesting that geographic sites probably play a role in this variation. It is interesting to note in this connection that the incidence of 7.2 per cent reported by Cole very closely approximates our figure of 6.94 per cent since both series come from the Great Lakes area, a well known 'goiter belt'. Hinton and Ford,³⁰ on the other hand, found the incidence of cancer to be 7.6 per cent in 184 cases of clinically benign nodular goiters from the Atlantic seaboard.

The high incidence of thyroid cancer as reported in the literature has been questioned by some. VanderLinn³⁷ recently approached the problem in a different manner. He reviewed the autopsy records of half a century in the Boston City Hospital and concluded that thyroid carcinoma as a cause of death at least was extremely rare, having found only 5 instances in a series of 18,668 autopsies. He went further and compared the conclusions drawn from surgical material as reported by Cole and co-workers with those of Jaffe drawn from autopsy material, both reports coming from the Chicago area. Applying Cole's findings to Jaffe's, it was concluded that thyroid carcinoma should be present in approximately 2 out of every 100 autopsies, whereas actually Jaffe found a ratio of 2 out of every 1,000 autopsies.

It should be emphasized that one might well expect significant statistical differences in comparing the incidence of malignancy in surgical material to a similar incidence in thyroid glands removed at autopsy. The selective forces producing these two groupings are obviously not identical.

The diagnosis of adenomatous goiter is made far more frequently on autopsy material than from clinical examination and for obvious reasons. In this respect it is interesting to consider a recent report by Martin.⁴² He reviewed a series of 100 subjects aged 45 years or over coming to autopsy in East Anglia where endemic goiter is not unduly prevalent. In 59 per cent he found diffuse colloid and nodular changes. In only 7 of the subjects were nodules detected by external examination. In 22 adenomas were found only on pathologic examination even though some were three-fourths inch in diameter.

With this in mind it was felt desirable to compare our clinical grouping as summarized in Table I with a subsequent grouping based on operative and pathologic findings as summarized in Table II. It is quite apparent from Table II that in this hospital at least not only are nodules overlooked at clinical examination, but not infrequently nodules are described where none exist.

TABLE II COMPARISON OF CLINICAL GROUPING TO OPERATIVE AND PATHOLOGIC FINDINGS

	Single nodule	1
	No nodules found	33
(b) Single nodule (103)	Single nodule	21
	Multiple nodules	1-6
	No nodules	2
Group II	Clinically palpable diffuse goiter (441)	
	No nodules	317
	Multiple nodules	12
	Single nodule	4
Group III	Clinically nonpalpable (16)	
	No nodules found	0
	Multiple nodules found	16

TABLE III SEX INCIDENCE

NO OF PATIENTS	CANCERS		PER CENT MALIGNANT
	NO	PER CENT	
	48	48.7	4.64
	17	21.1	4.44
	65		4.6

When only the adenomatous goiters are considered cancer was found in 1 of approximately every 10 females and 1 of every 11 males (Table I). While this limitation increases the apparent liability to malignancy among males with adenomatous goiters as compared to females this difference is far less than reported elsewhere. Ward,⁵⁴ in a similar manner, found carcinoma once in every 17 males as compared to once in every 44 females. Tindler,⁵⁵ while confirming the fact that the total number of cancers was greater in females found that given an equal number of goiterous men and women the men were about twice as likely to develop cancer.

AGE DISTRIBUTION

More than five sixths of the cancers in this series occurred in patients beyond the third decade with a preponderance in the fifth decade. The youngest patients were three females aged 17 years the oldest was a female aged 76 (See Table IV).

That youth does not exclude the possibility of thyroid cancer has been well emphasized by many investigators.^{51, 52, 53, 54, 55, 56} Kennedy⁵² called attention to the fact that an palpable mass in the thyroid gland of a child innocent

TABLE IV AGE DISTRIBUTION

AGE (yr.)	FEMALES	MALES	TOTAL
0-10	0	0	0
11-20	5	1	6
21-30	4	0	4
31-40	10	0	10
41-50	13	0	13
51-60	9	0	9
61-70	5	0	5
71-80	2	0	2
81-90	0	0	0
			(1)

reviewed the goiters in children 14 years of age or less encountered from 1908 through 1943 at the Mayo Clinic. During this period 53 children with nodular goiter were operated upon and in 18 instances the nodularity proved to be due to cancer. This astonishing incidence of approximately 34 per cent malignancy emphasizes the great hazard presented by nodular goiter in children.

RELATION TO HYPERTHYROIDISM

It has been our experience in this hospital that hyperthyroidism is of no aid whatsoever in the differential diagnosis of malignant goiter. In an earlier report Coller¹⁴ found abnormally high basal metabolic rates in 46 per cent of the individuals having malignant goiter. In the present series 26 per cent exhibited unequivocal symptoms of hyperthyroidism clinically and had elevated basal metabolic rates.

In general this has been the experience of most authors on the subject. In Simpson's series³ over one half of the patients exhibited clinical hyperthyroidism. Pemberton¹⁵ found the basal metabolic rate normal in 53.9 per cent, elevated in 33.0 per cent and below normal in 12.6 per cent. In Cattell's recent series⁵ 26 patients operated upon for hyperthyroidism were found to have unsuspected carcinoma.

In an excellent dissertation on primary carcinoma in exophthalmic goiter Gotsch²² reported 9 instances of carcinoma associated with hyperthyroidism. That the origin of the neoplasms was demonstrably associated with minute adenomas in some instances (and in fact probably in all) in no way detracts from the fact that these are all instances of malignancy coincident with hyperthyroidism.

Clute and Albright⁹ some time ago pointed out that hyperthyroidism may occur in patients with solitary discrete adenomas and that enucleation of the adenoma alone may allay the manifestations of hyperthyroidism. Cope and co-workers¹⁷ have recently given striking proof of the truth of this contention by comparing the physiologic activity of the adenoma and the uninvolved thyroid gland tissue with respect to their ability to inactivate thyroid stimulating hormone as well as their avidity for tracer doses of radioactive iodine. Poppel and associates¹⁶ carried out similar investigations though with dissimilar results. However they were dealing with diffuse disease whereas Cope and co-workers were dealing with localized disease.

PATHOGENESIS

While the immediate cause of thyroid malignancy remains obscure, it is generally agreed that most if not all, thyroid carcinomas originate in adenomatous foci. The term "thyroid adenoma" however, has been used rather loosely in referring to true adenomas and to nodular aggregates resulting from hyperplasia and involution. Clinically it is perhaps best to refer to all thyroid nodules by the term "nodular goiter" and reserve further differentiation for the histopathologist.

Warthin²² believed that true adenomas are congenital disturbances of development and are never formed in extrauterine life. He further identified the true adenomas as always present at birth in the form of very minute sharply circumscribed, encapsulated atypical portions of thyroid tissue with abnormal vascular relations. He distinguished pseudoadenomatous nodules of involution from true adenomas by their lack of a definite capsule and their normal acinous and vascular relationships. He also believed that the majority of primary carcinomas of the thyroid if not all, take origin from true adenomas.

Lahey, Hare and Warren²³ required the following criteria for identification of a true adenoma:

- 1 Complete encapsulation
- 2 Homogeneous texture grossly and microscopically throughout with the exception of degenerative foci such as cysts, calcification or fibrosis
- 3 Distinct variation of the tissue within the capsule from that outside the capsule
- 4 Evidence of compression of adjacent tissue by the nodules

They classified adenomas into four major groups according to their differentiation as determined from the histologic appearance as follows:

- 1 Embryonal adenoma
- 2 Fetal adenoma
- 3 Simple adenoma (including Hurthle cell adenoma)
- 4 Colloid adenoma

The embryonal type is the least differentiated resembling the structure of the thyroid gland of early embryonic life and made up of solid columns of small, compact polyhedral cells. Because of this pattern they are sometimes referred to as 'trabecular adenomas'.

The fetal type (as the term is used here) represents a more differentiated form than the embryonal type. On section the follicles resemble rosettes are considerably smaller than those of the normal thyroid and contain only a small amount of colloid. This type is sometimes referred to as 'tubular adenoma'.

The simple adenoma resembles more closely the structure of normal thyroid tissue, the acini are within normal range of size and are lined by cells varying from cuboidal to columnar. This type is sometimes referred to as 'microfollicular adenoma'.

The Hurthle cell type as described by Lahey and co-workers is characterized by the presence of acini lined with large pale clear acidophilic cells

with large prominent vesicular nuclei. This type is not recognized as a distinct entity by most writers. Eosinophilic staining is not infrequently seen by pathologists in a variety of conditions of the thyroid. Wilensky and Kautman¹¹ suggested that the evidence at hand indicates a physiologic rather than an anatomic basis for the appearance of the so-called Hurthle cell in normal thyroid and that the so-called Hurthle cell does not represent a distinct anatomic unit but rather a functional change probably nutritive. They favored discarding the term 'Hurthle cell tumor'.

The colloid adenoma is the most differentiated type. On section the veins are greatly distended with colloid and the acinar epithelium is usually low cuboidal or flat. This type is sometimes referred to as "microfollicular adenoma." Clute and Albright¹² classified all thyroid adenomas as either parenchymatous or colloid in form. The former are characterized by a quantitative preponderance of epithelial elements over colloid secretion and stroma; the latter are characterized by large follicle formation with abundant colloid and stroma. These authors pointed out that different stages of development and differentiation, that is both parenchymatous and colloid characteristics may occur in different parts of a single adenoma.

Brenizer and McKnight¹³ felt they could identify true adenomas from colloid inclusions by observing that with true adenomas they were able to strip the cellular mass more readily from the capsule. Hertzler¹⁴ distinguished sharply between the bosselations of nodular goiter and true congenital tumors or fetal adenomas stressing the independent origin of the latter and the fact that they never regress. Their ultimate fate in Hertzler's opinion, is usually one of gradual degeneration and, less commonly gradual progression to malignancy.

In contradistinction to true adenomas the nodules most frequently found in adenomatous goiter are the result of repeated stimulation of the gland under the influence of various factors followed by involution and colloid storage when the stimulus is withdrawn. A gland once stimulated to hyperplasia probably never returns entirely to normal. More often than not both the hyperplastic and involutionary sequences are not uniformly distributed throughout the gland. Areas begin to appear in which hyperplasia is greater and involution minimal leading to development of irregularly scattered nodules of varying size. It is felt by many authors that such nodules are not in the nature of new growths either clinically or histologically and are rarely, if ever, related to the origin of thyroid cancer.

The stimuli capable of initiating these cyclic changes in the thyroid are numerous. Physiologic stimuli of such nature are observed at puberty during menses and in pregnancy. The latter factors are cited frequently to account for the greater incidence of nodular goiter in females. Hyperplasia induced by infection and toxemia has been discussed by Cole, Womack and Gray.¹⁵ More recently various chemicals have been demonstrated to be capable of producing interesting and important forms of goiter. These have included methylated purines, thiocyanates, methyl cyanide, thiourea, and various thiourea derivatives, the sulfonamides and related compounds.¹⁶

Womick and Cole¹¹ realizing that it was possible to produce hyperplastic changes experimentally and at the same time to cause artificial involution by the use of iodine (or 'natural' involution by withdrawing the stimulus), made some significant observations on the anatomic changes occurring in the thyroids of dogs subjected to such cyclic influence. Hyperplasia was induced by three forms of stimuli: (1) the production of infections; (2) the injection of methylated purines; and (3) the implantation of contaminated foreign bodies over a long period of time. By such means they were able to demonstrate the formation of small adenomas formed apparently in proportion to the amount of fibrosis induced in the gland. Perhaps their most startling observation was: 'Some of these nodules resembled the so-called fetal adenoma in such detail that while we cannot disprove the theory of embryonic rest we are inclined at the present time to explain the presence of these nodules on the basis of morphologic changes as a result of a natural physiologic cycle. Although we have no proof that these adenomas were not already present in microscopic form before our experiments were started we wish to emphasize the fact that in sections taken from several hundred normal dogs in the past few years we did not encounter a single instance of adenoma.' The reference to the theory of embryonic rests used here harks back to a theory propounded by Wölfler concerning the origin of true adenomas. It was Wölfler's contention (in accordance with Cohnheim's theory of the origin of tumors from congenital *Anlagen*) that adenomas had their origin from undifferentiated epithelial cell rests which had not been utilized in the formation of the normal gland and assumed an intercalary position. Some years ago Rienhoff¹² employing paraffin wax models of the thyroid gland reconstructed from serial sections concluded that what Wölfler observed was in reality tangential sections through the dome of an underlying follicle, giving the appearance of an isolated group of epithelial cells. He was unable to demonstrate the presence of fetal cell rests between normal adult follicles. It was Rienhoff's impression that the concept of fetal cell rests evolved from inept methods leading to inaccurate conclusions. Wölfler working during the twilight of the nineteenth century, had to contend with poorly stained thick sections and without the advantage of serial cuttings.

Other theories concerning the origin of adenomas include the theory of dedifferentiation or reversion of the follicular cell to a more embryonic thyroid epithelial cell from which an adenoma might arise; also the theory offered by Goetsch that the true adenoma probably has its origin in certain cells which occur in the normal and hyperplastic follicle and are known to have the characters of fetal or embryonic cells. Goetsch asserted that these occur not uncommonly singly or in pairs interposed between follicle lining cells of the hyperplastic gland and may be differentiated from the remaining cells of the follicle by their differences in size, shape, and in the nature of the mitochondria which their protoplasm contains.

The role of the so-called lateral aberrant thyroid nodules in the pathogenesis of thyroid cancer remains particularly controversial. It is now gener-

ally agreed that the thyroid gland of man is derived from one median and two lateral primordial structures⁴⁴⁻⁶. The median component originates as a diverticulum from the pharynx and migrates caudad along a path ventral to the pharynx. Almost from its initial appearance it is a bilobed structure and in the definitive position reached during the seventh week consists of two distinct lobes one on either side of the midline joined by a narrow isthmus. The point of origin remains marked by the foramen cecum. Developmental anomalies related to this migration such as lingual thyroids and thyroglossal duct cysts are seen quite frequently. Far less commonly cancers have been observed to originate in such anomalies. Thus squamous cell carcinomas of presumable thyroglossal duct origin have been described⁴⁶⁻² and in the series reported by Watson and Pool¹ primary cancer developed in lingual thyroid tissue in 3 instances.

The lateral components according to Patten⁴⁴ develop as small diverticula on the caudal free of the fourth pharyngeal pouch. These diverticula break loose from the fourth pouch and become incorporated with the lateral lobes of the median component as the latter reaches the posterior pharyngeal levels in its migration caudad. Some authors regard these diverticula as rudimentary fifth pharyngeal pouches. Others convinced that they form true thyroid tissue prefer to identify them as lateral thyroid primordia. Patten though asserting that evidence in favor of the latter view is increasingly strong suggests that until their significance is established beyond doubt they might better be designated by the noncommittal term postbranchial bodies.

According to Weller² the median component at the time of fusion, is composed of more differentiated tissue than the lateral contributions but subsequently the median component undergoes little change except growth until both components are similar in appearance whereupon the epithelial sheets undergo differentiation into follicles throughout the entire gland.

Single or more frequently multiple nodules are observed in the lateral cervical region (for the most part) which in microscopic section appear as papillary adenomas and occasionally frank papillary thyroid carcinomas. That there is considerable diversity of opinion regarding the origin, pathogenesis and potential hazards of these lateral nodules has been adequately emphasized recently by Graham². Labey²⁻³ regarded them as lateral aberrant thyroid masses associated with developmental anomalies of the lateral primordia. He felt that they are all either malignant or potentially malignant and consequently require radical surgical treatment followed by intensive radiation. In an earlier discussion Labey²² explained the occasional coexistence of a similar (papilliferous) nodule within the thyroid gland as probably representing a metastasis from lateral aberrant thyroid masses. More recently²³ however he has stated that such a coexistence could be explained on embryologic grounds without spread or metastasis in either direction. He would now regard the papilliferous nodule within the thyroid gland as representing a lateral aberrant nodule (fused with the thyroid) which had failed to undergo atrophy. Crile²⁻⁵ has summarized his experiences with respect to papillary

tumors in two excellent successive papers. In the earlier report Crile¹⁸ regarded such tumors as multiple, primary, relatively benign or locally malignant lesions arising in some developmental disturbance associated with the lateral thyroid derivatives. While concurring with Lihey for the most part as to the origin of these tumors even in this earlier report Crile considered x-ray therapy as ineffectual in their treatment placing reliance on surgical removal.

Another view, as expressed by Kim¹⁹ and Pemberton^{20, 21} holds that "lateral aberrant thyroids" are in reality metastatic carcinomas in cervical lymph nodes having metastasized there from a primary carcinoma in the homolateral lobe of the thyroid proper. Their evidence on the whole is rather convincing. They accordingly recommend radical block dissection of the neck with removal of the corresponding thyroid lobe whether or not a tumor can be felt or seen in that lobe at time of operation. They regard radiation therapy as of questionable benefit unless surgical removal of the diseased tissue has been incomplete.

Watson and Pool²² reported several cases related to this problem which tend to support the view of Kim¹⁹ and Pemberton. They reported having seen extensive unilateral or bilateral cervical chains of carcinomatous thyroid tissue in several of their cases which first led them to suspect origin in multiple aberrant thyroid rests. However, when small unsuspected primary foci of carcinoma were found in the thyroid gland itself they withdrew their original contention and in only one questionable instance could they suspect the primary disease as of aberrant thyroid origin.

Crile's most recent review of the subject⁶ deserves particular attention. While not entirely abandoning his earlier theory that in some cases at least lateral cervical nodules are possibly multiple primary tumors of benign behavior, Crile later regarded these cervical nodules as probably representing metastases from a primary tumor of the thyroid. In 16 consecutive cases of papillary tumors of the cervical region when the thyroid was carefully examined a primary papillary neoplasm was found in the thyroid. Crile emphasized that the primary tumor may be very small difficult to palpate and occasionally not discovered until the gland is rotated out of its bed to expose the posteromedial surface, an area avoided by many surgeons. Unless the gland is explored thoroughly, a small primary may easily be left behind and lateral cervical tumors may continue to form yet the primary may not enlarge appreciably over a period of many years. Crile again stated that in the few cases in which x-ray therapy had been given the results were disappointing whereas surgical excision of the primary and metastasis had given excellent results.

Certainly the evidence that most of the so-called lateral aberrant thyroid tumors are in reality metastases is so convincing that all patients with ectopic thyroid tissue should have a thorough examination of the thyroid gland and perhaps a homolateral lobectomy in all instances.

Oddly enough in our series there was but one questionable instance of lateral aberrant thyroid nodules. Another possible consideration in the pathogenesis of thyroid carcinoma involves the prophylactic use of iodine.

Warthin⁵⁰ summarized his observations as follows: "proliferation of the adenoma cells appears to result from over iodination. A peculiar hypertrophy of the adenoma is produced, and transitional stages between such hypertrophic proliferating adenomas and carcinoma have been observed. It is an open question whether the over use of iodine may not stimulate the development of carcinomatous transformation of an adenoma in a patient possessing also the cancer susceptibility constitution."

Moreover since the introduction of thiourea derivatives in the management of hyperthyroidism, an even more disturbing correlation has possibly been observed. It is now generally believed that thiouracil ameliorates the symptoms of thyrotoxicosis by action outside of the gland. In fact within the gland the associated changes closely resemble the histologic picture of the hyperplastic gland of preiodine days. One sees on cross section extreme hyperplasia with heightened epithelium, marked papillary infolding and mitoses in the epithelial cells.⁵¹ Because of these cellular changes fears have been expressed of the possibility of inducing malignancy and it has been suggested that the drug be used only as a preliminary medication in preparing the patient for thyroidectomy particularly in the presence of nodular changes within the gland.^{22, 40, 43, 53}

Experimental studies carried out in Great Britain^{2, 3} and tersely summarized in a recent editorial would seem to carry the correlation beyond mere speculation regardless of how critical one wishes to remain. In 1941 Wilson and associates⁴⁴ reported the discovery of an extraordinarily powerful carcinogen 2-acetaminofluorene which, when fed to rats was capable of producing astonishingly frequent neoplasms in the organs and tissues of animals having a relatively low incidence of spontaneous occurrence of tumors. Pielchowsky in Great Britain² not only confirmed their discovery but also carried it a step further in regard to thyroid cancers.³ It had been observed in these experiments that none of the animals developed tumors of the thyroid gland despite the high incidence of neoplasms in other organs. With this in mind Pielchowsky first induced intense hyperplastic changes in the thyroid gland by feeding his animals thiourea. Upon subsequently feeding them acetaminofluorene he was able to demonstrate the appearance of invasive epithelial tumors within the thyroid gland. Apparently antecedent or concurrent hyperplasia was a necessary and decisive factor in the production of these thyroid tumors.

The question has been editorially raised²² May not thiouracil similarly fortify the cancer susceptibility factors (as yet unknown) leading to a higher incidence of malignancy in the human thyroid?

DIAGNOSIS

Most authors emphasize the fact that there are no reliable signs and symptoms upon which to make an early diagnosis of thyroid cancer.^{20, 43, 51} In the late cases the diagnosis may be only too obvious. Consequently any diagnostic aids that might prove helpful in evaluating these cases are worthy of mention. A preoperative laryngoscopic examination should be

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Some years ago in a personal communication to Coller¹⁴ these criteria were epitomized by Warthin as follows

The usual criteria of malignancy—changes in cell type and staining reaction, alteration in function as shown by the disappearance of colloid, abnormal architecture, infiltration of surrounding tissue, inflammatory reactions about the neoplasm, extension into lymphatic and blood vessels, abnormal retrogressive changes in the parenchymatous cell of the new growth and finally metastases—all of these apply to the diagnosis of thyroid carcinoma as in malignancy in other organs. To any one familiar with the cytologic changes in the thyroid, particularly those associated with exophthalmic goiter, the differential diagnosis of malignancy using the ordinary criteria presents no especial difficulty in the case of the great majority of thyroid cancers. It must be remembered, however, that an experienced pathologist may mistakenly diagnose the typical parenchymatous hypertrophy of exophthalmic goiter as adenocarcinoma or papillary adenocarcinoma. Such mistakes are by no means rare. Only in the case of malignant adenoma colloid in which the structure of the neoplasm may closely imitate that of normal gland structure is there likely to be any difficulty in the diagnosis. When metastases of such malignant adenomas are found in the bones or in other tissues, the fact that they are out of place is sufficient for the diagnosis. A study of numerous blocks from the primary lesion in the thyroid will always reveal local evidence of malignancy, particularly the invasion of normal thyroid tissue by the atypical acini and their extension into the lymphatics and veins in the trabeculae of the gland. Graham's criterion of growth into blood vessels would apply in this case but in the great majority of cases of thyroid cancer such a criterion of malignancy is not necessary to the correct diagnosis and in many cases extension into the blood vessels will not be found. It must be emphasized here in this connection that hematogenous metastasis is not common in cases of thyroid carcinoma until cervical and mediastinal nodes have reached a large size. The early hematogenous metastasis into bones and lungs are relatively rare.

CLASSIFICATION

The classification of thyroid neoplasms has been no less controversial than the microscopic criteria of malignancy. The practical value of any classification would appear to repose in how closely it correlated the recognizable histopathologic features with the clinical course of the disease. Perhaps too much emphasis has been placed on classification since, as is true of so many neoplasms, it is not uncommon to find several types represented in different areas of the same specimen. Moreover, imperceptible gradations from one type to another as well as intermediate forms constitute common findings.⁸ (In such cases it is the usual practice arbitrarily to classify on the basis of what is believed to be the most malignant type represented.)

The classification used by Iley, Hare and Warren³⁵ is one frequently adopted by others.^{11, 42}

Group I—Low or Potential Malignancy

- (1) Adenoma with blood vessel invasion
- (2) Papillary cystadenoma with blood vessel invasion
 - (a) Originating from thyroid
 - (b) Originating from aberrant thyroid

son and Pool impressed with the possibility that he is dealing with thyroid cancer, should not hesitate to proceed with a suitable operation in the best interests of the patient irrespective of the frozen section report.

In the differential diagnosis of lesions most likely to be mistaken clinically for thyroid cancer or vice versa one should consider (1) Benign nodular goiter, (2) sudden hemorrhage, (3) acute thyroiditis (4) chronic thyroiditis (Hashimoto and Riedel types), (5) calcareous infiltration and (6) chronic infective granulomas.

In this series of the 56 epithelial neoplasms the diagnosis was made clinically in only 8 instances. Malignancy was clinically suspected and confirmed at operation in 8 instances, it was not suspected both clinically and at operation in 39 instances and in 1 instance malignancy was not suspected clinically, was not found in the specimen removed at operation, but found in the remnant left behind when the patient came to autopsy (postoperative death).

All 5 of the cases diagnosed ultimately as sarcomas were either diagnosed clinically as cancer or were strongly suspected of cancer. This diagnosis was unequivocally made clinically in 3 instances and confirmed at operation in the others. In no instance was the sarcomatous nature suspected until the microscopic reports became available.

The microscopic diagnosis of thyroid cancer has long been a source of contention among pathologists. The nature of a tumor that exhibits destructive infiltrative growth or that gives rise to distant metastases, one that recurs following excision or kills the host is now rarely in doubt. Differences of opinion arise in respect to the interpretation of early malignancy.

Graham²⁶ after a painstaking review of the problem, emphasized the importance of blood vessel invasion as not only an absolute criterion but indeed the only criterion of malignancy in respect to some encapsulated nodules.

Warren²⁷ found that in 1080 cases of surgically removed adenomas not showing blood vessel invasion none gave evidence of malignancy from $2\frac{1}{2}$ to 7 years following operation. Whereas of 34 patients who did show blood vessel invasion 2 died (10 months and $2\frac{1}{2}$ years following operation) of local recurrence and multiple metastases.

While no one questions the accuracy or the significance of Graham's observations many experienced pathologists and clinicians alike have long felt that such criteria are too rigid and that the presence of blood vessel invasion is not necessary for the accurate diagnosis of thyroid malignancy.

Pemberton²⁸ called attention to the enlargement of the nucleolus (long recognized as a characteristic feature of malignant cells) and described a nucleolar nuclear ratio that may be employed as a measurable criterion of malignancy.

The pathologists in our hospital have always felt that the diagnosis of thyroid cancer should be based on the same criteria that are applied to cancer of all other organs and tissues. These are namely loss of differentiation, hyperchromatic nuclei, number of mitotic figures, presence of atypical mitotic figures and infiltrative growth.

Some years ago in a personal communication to Coller¹⁴ these criteria were epitomized by Warthin as follows:

The usual criteria of malignancy—changes in cell type and staining reaction, alteration in function as shown by the disappearance of colloid, abnormal architecture, infiltration of surrounding tissue, inflammatory reactions about the neoplasm, extension into lymphatic and blood vessel—abnormal retrogressive changes in the parenchymatous cell of the new growth and finally metastasis—all of these apply to the diagnosis of thyroid carcinoma as in malignancy in other organs. To any one familiar with the cytologic changes in the thyroid particularly those associated with exophthalmic goiter the differential diagnosis of malignancy using the ordinary criteria presents no especial difficulty in the case of the great majority of thyroid cancers. It must be remembered however that an experienced pathologist may mistakenly diagnose the typical parenchymatous hypertrophy of exophthalmic goiter as adenocarcinoma or papillary adenocarcinoma. Such mistakes are by no means rare. Only in the case of malignant adenoma colloid in which the structure of the neoplasm may closely imitate that of normal gland structure is there likely to be any difficulty in the diagnosis. When metastases of such malignant adenomas are found in the bones or in other tissues the fact that they are out of place is sufficient for the diagnosis. A study of numerous blocks from the primary lesion in the thyroid will always reveal local evidence of malignancy particularly the invasion of normal thyroid tissue by the atypical acini and their extension into the lymphatics and veins in the trabeculae of the gland. Graham's criterion of growth into blood vessels would apply in this case but in the great majority of cases of thyroid cancer such a criterion of malignancy is not necessary to the correct diagnosis and in many cases extension into the blood vessel will not be found. It must be emphasized here in this connection that hematogenous metastasis is not common in cases of thyroid carcinoma until cervical and mediastinal nodes have reached a large size. The early hematogenous metastases into bones and lungs are relatively rare.

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- (1) Adenoma with blood vessel invasion
- (2) Papillary cystadenoma with blood vessel invasion
 - (a) Originating from thyroid
 - (b) Originating from aberrant thyroid

Group II Moderate Malignancy

- (1) Papillary adenocarcinoma
- (2) Alveolar adenocarcinoma
- (3) Hurthle cell adenocarcinoma

Group III High Malignancy

- (1) Small cell carcinoma (carcinoma simplex)
 - (a) Compact type
 - (b) Diffuse type
- (2) Giant cell carcinoma
- (3) Epidermoid carcinoma
- (4) Fibrosarcoma
- (5) Lymphoma

The classification used by Penherton⁴⁰ is far more simple

- (1) Papillary adenocarcinoma
- (2) Adenocarcinoma in adenoma (malignant adenoma)
- (3) Diffuse adenocarcinoma
- (4) Epithelioma
- (5) Sarcoma

Watson and Pool⁴¹ divided thyroid cancers into six major groups. A further breakdown of each group is afforded on the basis of grading

- Group I Papillary adenocarcinoma
- Group II Small alveolar and solid large cell adenocarcinoma
- Group III Spindle and giant-cell carcinoma
- Group IV Small round-cell carcinoma
- Group V Metastasizing struma
- Group VI Lymphosarcoma

Similarly simple and eminently practical is the classification used by Ward.⁴² It is based on prognostic and therapeutic criteria

- Group I Papillary carcinomas
- Group II Malignant adenomas
- Group III All others including scirrhous small cell types undifferentiated carcinomas and those which display a sarcomatous tendency

A somewhat different type of classification is one proposed by Portmann.⁴³ It is based essentially on the extent of involvement. A notable feature of this classification is the fact that it affords a common denominator applicable to most popular classifications and thus affords a basis for comparative study. In brief the classification is as follows

- Group I Cases diagnosed only after microscopic examination
- Group II Cases in which diagnosis is suspected on the basis of the patient's age, recent rapid enlargement or discovery at operation (tumor still localized within the capsule of the gland)
- Group III Cases in which there is clinical or pathologic evidence that the neoplasm is invading or extending outside the capsule of the gland but without evidence of distant metastases
- Group IV Cases with evidence of distant metastases

In the present series there were 56 epithelial neoplasms or carcinomas and 5 sarcomas an incidence of 91.8 per cent and 8.2 per cent respectively. The 56 epithelial neoplasms in our series are according to Portmann's classification in Table VI.

TABLE V DISTRIBUTION OF PATHOLOGIC TYPES OF FIFTY-SIX EPITHELIAL NEOPLASMS

		NUMBER
Group I	Medullary Carcinoma (2)	
	(a) Diffuse type	11
	(b) Hypernephroid type	5
	(c) Malignant adenoma	4
Group II	Adenocarcinoma (29)	
	(a) Diffuse type	3
	(b) Malignant adenoma	24
Group III	Squamous Carcinoma (4)	
	(a) Ordinary type	2
	(b) Carcinoma type	2

TABLE VI DISTRIBUTION OF FIFTY-SIX EPITHELIAL NEOPLASMS ON THE BASIS OF PORTMANN'S CLASSIFICATION*

Group I	30
Group II	11
Group III	9
Group IV	3 (plus 1)

* One case not classified here because of the possibility that the regional foci were in fact aberrant thyroid tissue rather than carcinoma.

It is frequently asserted that most if not all so-called sarcomas of the thyroid are in reality highly anaplastic carcinomas. Uncertainty stems from the close microscopic resemblance of highly anaplastic epithelial cells to equally anaplastic supporting tissue cells.

That sarcomas of the thyroid do occur however cannot be denied since there has been a sufficient number reported whose sarcomatous nature cannot be denied.

They and associates¹ accepted but one criterion in identifying fibrosarcomas namely that of a typical sarcoma the cells of which show definite collagen or fibroglial fibrils. Pemberton² thought that the incidence of sarcoma as reported in the literature is far too high. In his series of 774 thyroid cancers the diagnosis of sarcoma was established in but 4 instances. Batts³ reported an osteogenic sarcoma arising in the thyroid and found 7 other cases reported in the literature. One of these occurred in the series reported by Pemberton.⁴ Jovic and co-workers⁵ reported a liposarcoma of thyroid origin. Simpson's⁶ series contained 5 sarcomas a proportion of 1 sarcoma to 10 carcinomas.

The 5 sarcomas in our series were all diagnosed as the spindle cell type.

METASTASES

Metastases were observed in 9 instances in this series. The most frequent site of involvement was the lungs pulmonary metastases being observed in 6 cases. Other sites included cervical lymph nodes the mediastinum skull pelvis brain and adrenals.

Pemberton⁴⁰ and Horn and co workers⁴¹ found the highest incidence of involvement to be in the cervical lymph nodes. Pemberton also found a marked predilection of papillary adenocarcinoma to spread to cervical lymph nodes.

Ward³⁸ emphasized the fact that following removal of the primary tumor pulmonary metastases will occasionally lie dormant for many years. One of his patients was alive and in apparent good health 13 years after the lungs had been observed to be riddled with milium nodules. Moreover numerous examples can be found in the literature of patients living in apparent good health for many years following removal of isolated metastatic nodules and subsequent thyroidectomy. Ward³⁸ pointed out that in some cases the primary lesion may be microscopic in size and identified only after serial section of the entire gland. Failure to recognize this fact has probably been responsible for the not infrequent reference to so called 'benign metastasizing goiter' in earlier reports. Simpson⁴² some years ago made a comprehensive study of the subject and proved quite conclusively that there was no basis in fact for the contention that such foci represented aberrant thyroid tissue. He urged that the term 'benign metastasizing goiter' be abandoned as confusing and erroneous.

Metastases to the thyroid gland itself are extremely uncommon. In the present series there was 1 instance (not included in our total) in which a thyroid nodule proved to be a metastasis from a breast carcinoma. Linton⁴³ recently reported a case in which a hypernephroma metastasized to the thyroid gland. He was able to find 17 other such cases in the literature. It is interesting in this connection to observe that Simpson in reviewing the problem of primary thyroid carcinoma resembling hypernephroma called attention to the fact that such tumors on occasion have been erroneously interpreted as metastases to the thyroid.⁴²

PROGNOSIS

As pointed out by Watson and Pool⁴⁴ in considering the end results and prognosis of thyroid carcinoma it is well to speak of survival rather than 'cure' rates. This is necessarily so since it is well known that the disease may exhibit recurrence or metastases long after apparent cure. Watson and Pool reported 2 instances of total recurrence 16 years following treatment. Rosh and Raider⁴⁵ also reported a case in which metastases appeared 16 years after operation. Numerous similar examples are readily found in the literature.

Ward³⁸ based prognosis upon three principal factors: (1) the time of diagnosis, (2) the pathologic pattern and (3) the presence of metastases. Deaths occurred in direct proportion to the ease of diagnosis. Thus there was a 20 per cent 5 year survival rate in those diagnosed or suspected preoperatively and an 80 per cent 5 year survival in cases in which the diagnosis was first made by the pathologist.

In Ward's series the presence of a papillary pattern offered by far the best prognosis; indeed the degree of malignancy could apparently be estimated by the extent of departure from this pattern.

Kroger,³⁶ in reviewing carcinomas forming the spindle cell pattern came to the conclusion that this particular variety was seemingly completely resistant to both surgical and radiation forms of therapy.

In the present series all 5 of the patients upon whom the diagnosis of sarcoma was made were dead within 1 year, indeed, 4 of them were dead within 4 months following operation.

The survival rate of the 56 patients having epithelial neoplasms was analyzed on the basis of Portmann's classification.

Group I Included 30 cases. At the time this analysis was made 22 of this group were still living. 8 had died. Of the 22 living 5 were alive and free of recurrence for a period of 10 years or longer. 14 for a period of 5 years or longer, the remaining 3 had an elapsed survival time of less than 5 years. Of the 8 who had died, there was a question of recurrence in but 1 instance. This patient died elsewhere some 7½ years following operation and no autopsy was obtained. All others died of causes other than cancer.

Group II Included 11 cases. At the time this analysis was made, 7 of this group were still living. 4 had died. Of the 7 living 1 was alive and free of recurrence for a period of 11 years. 4 for 5 years or longer but less than 10 years, and 2 for less than 5 years. Of the 4 who had lived there was 1 instance of death by violence while the remaining 3 died of recurrence with distant metastases (7 months, 3½ years and 5 years respectively following operation).

Group III Included 9 cases. At the time of this analysis 3 of this group were alive. 6 had died. Of the 3 living survivors all have passed the 5 year period.

Of the 6 who had died there was 1 instance of death by cerebral hemorrhage without evidence of recurrence. The remaining 5 died of obvious recurrence within 9 months following operation.

Group IV Included 5 cases. 1 case being purposely omitted since it was the only instance in this series of a possible lateral aberrant thyroid origin. If the cervical nodules are regarded as metastases then this case would belong in Group IV, and the total number of cases would be 6. The patient in question was alive and well 5 years following surgical removal of the cervical nodules and the homolateral lobe. Considering these 5 cases at the time of this analysis only 1 was living. 4 had died. The lone survivor had passed the 4 year period but had a probable pelvic metastasis. The 4 deaths were all due to obvious recurrent thyroid neoplasm. All were dead within less than 3 years following treatment. It is interesting to note that 1 case showed at autopsy multiple tertiary carcinomatous nodules throughout both lungs which had been observed on roentgenologic examination just before death. It is quite apparent from this analysis that Portmann's classification (based on the extent of the disease) has definite prognostic significance. Horn and associates³⁷ reported an essentially similar experience in their series. The operative mortality in this hospital was determined for the last 3 year period. The operative mortality for

all thyroidectomies (including hopeless malignant goiters where surgery was limited to lifesaving tracheal decompression) was 1.56 per cent if thyroid cancer is excluded the operative mortality was 0.3 per cent.

TREATMENT

The evaluation of operability and the extent of the operative procedure to be undertaken will always vary with the skill and experience of the surgeon.

Pemberton¹⁰ felt that operability depends on the extent of the local invasion of the primary lesion and the absence of distant metastases. Tumors that are completely fixed should not be operated upon since the risk of extirpation would be out of proportion to the amount of benefit one could hope to derive. When mobility is limited in Pemberton's opinion exploration is justifiable even though the tumor cannot be completely removed since this permits direct radium application to the fragments left. In his experience this procedure was particularly effective in the treatment of papillary carcinomas. Pemberton cited several instances of individuals living many years without evidence of recurrence following treatment by incomplete excision supplemented with radiation therapy. He regarded this combined form of therapy as the most effective form of treatment available depending on the type and grade of malignancy.

At the Lahey Clinic postoperative irradiation is used in all cases of thyroid cancer regardless of the pathologic type or the extent of involvement.¹¹ In the management of so-called lateral aberrant thyroids Lahey and co-workers⁸ and more recently Cattel⁶ recommended radical neck dissection plus removal of the homolateral thyroid lobe. With regard to discrete adenomas Lahey felt that it is unnecessary to do more than a complete excision of the adenoma with its capsule intact. When erosion of the capsule and involvement of the pyramidal gland have occurred the entire lobe and isthmus together with the contained neoplasm are removed intact. The attitude of the Lahey group toward the management of more extensive neoplasms has recently become more optimistic.⁸ In former years they were content to prove the diagnosis by biopsy and rely on radiation therapy. At present they believe that as much of the neoplasm as possible should be removed, tracheotomy performed and intensive postoperative irradiation therapy instituted. Radical neck dissection is eschewed in extensive cases. Irradiation therapy is started as soon as the patient's condition warrants it usually within one week. They have felt that there need be no concern regarding failure of healing even after a 3 day period has elapsed. While on the whole results in these advanced cases continue to be poor there is an occasional long survival.

As stated previously Cattel¹² reported papillary tumors of the thyroid and of lateral aberrant thyroid origin as singularly benign in most instances. He preferred to treat these lesions by surgical excision. Moreover local recurrences following incomplete operation are also treated by reoperation rather than by irradiation therapy.

In this connection it is interesting to note Graham's¹³ experiences with local recurrences in the veins of the neck without detectable evidence of distant

metastases. The local recurrence presumably arises in a remnant of tumor tissue reposing in an isolated venous segment that was overlooked at the original operation. The most effective treatment of such recurrences proved to be a properly planned surgical removal. Radium and roentgen therapy proved ineffectual both in preventing such recurrences and in curing them. The radical operation for malignant thyroid tumors described by Crile and Crile¹ was designed in part at least, to minimize or prevent such recurrences and is a well planned procedure.

Ward² considered the therapeutic problem from three phases: prophylactic, definitive and palliative. Simple enucleation of adenomas is frequently regarded as adequate prophylactic treatment. However, Ward confessed his regret upon occasion at not having originally performed lobectomy or subtotal thyroidectomy upon receiving the pathologist's report of malignancy in the enucleated specimen. In selected instances of this kind Ward believed the surgeon to be justified in immediate reoperation to remove the involved lobe and suspected soft tissue in the neighborhood. In one such case carcinoma was demonstrated in the specimen removed at the second operation and the patient remained well for over 15 years. In instances where carcinoma is suspected preoperatively Ward recommended that a radical operation be planned employing the type of operation recommended by Crile and Crile. Regardless of the type of anesthetic employed Ward recommended the use of an intratracheal catheter with inflatable cuff. Mediastinal extension in his experience often proves to be an unsurmountable obstacle to complete removal of the tumor. He has found irradiation therapy to be of little value except for papillary carcinomas and in a small number of malignant adenomas. In dealing with large and small cell anaplastic carcinomas or the so called carcinosarcomas he found both surgery and irradiation ineffectual. Metastases if not too widespread and fulminating are given a trial of irradiation; the papilliferous types usually respond well whereas malignant adenomas show little response. Local recurrent nodules are removed surgically.

Horn and associates³ favored a combination of surgery and irradiation in the treatment of lateral aberrant nodules. Surgical removal has been the initial treatment of choice. In general, they have found irradiation therapy of value though recognizing that permanent cures may never be assured by this means. It has been their policy to wait 2 to 3 months following surgery before initiating irradiation therapy in order to permit physiologic repair to take place. When the surgical procedure is limited to simple exploration and biopsy, irradiation is started immediately. In treating patients with pulmonary metastases they urged extreme caution since in their experience the presence of metastatic carcinoma renders the patient especially susceptible to radiation pneumonitis. Their data support the opinion of Portmann that routine postoperative irradiation therapy does not clearly benefit the patient with malignant adenoma or papillary carcinoma which has been discovered only on pathologic examination and is confined within a capsule. Their clinical experience led them to believe that all other patients should receive irradiation.

Watson and Pool⁴¹ described a technique of radical thyroidectomy combined with neck dissection which is carried out under local Novocain infiltration and cervical nerve block anesthesia. In a series of 12 such radical procedures there was no death. Mention has already been made of their use of aspiration biopsies in planning the extent of the surgical procedure. Their experience led them to conclude that thyroid cancer cannot be classed as a radiosensitive lesion. They felt that it responds best to a combination of surgery and interstitial radiation in the form of gold filtered radon seeds. In far advanced cases palliative operative procedures for temporary relief of dyspnea and dysphagia were attended by a high operative mortality, for example tracheotomy was followed by death in 50 per cent of 14 cases.

Rosh and Rander⁴² discussed irradiation therapy. They treat all thyroid cancers to skin tolerance and repeat the series, if the skin is in satisfactory condition, within 6 to 8 weeks. Residual tumors following the second series are treated by gamma rays in the form of a radium pack or a collar containing radium tubes.

Several authors have observed that occasionally a lesion previously considered inoperable becomes operable following palliative irradiation therapy.^{43 44 45}

Because of the relatively high incidence of unsuspected malignancy in apparently benign nodular goiters the early removal of all such goiters is strongly recommended in this hospital. Moreover, additional considerations have been cited frequently enough to make us seriously doubt that any nodular goiter should ever be regarded as innocent.^{9 10 11 12 13 14} Among these additional considerations the ones most frequently mentioned are the development of pressure symptoms, the development of hyperthyroidism (which appears in particularly significant instances after the third decade), and the definite cardiovascular damage which appears in at least one quarter of those with hyperthyroidism and in a smaller but appreciable number of those with normal metabolism. In the group with normal metabolic rates the development of symptoms is notoriously insidious. However, the improvement in health of many of these patients following thyroidectomy has convinced many clinicians that unrecognized toxicity or an altered secretion is frequently associated with nontoxic nodular goiters. The basal metabolic rates following removal of nontoxic goiters remain essentially what they were prior to operation.

In general, the stage and extent of the disease determine the magnitude of the surgical procedure carried out. It has been the practice in this hospital to carry out relatively radical subtotal thyroidectomies on all nodular goiters. Enucleation procedures are generally eschewed since it has been our experience that adenomas are usually multiple and it is extremely difficult to palpate intraglandular nodules. In consequence of this attitude the initial operation frequently proves sufficient for the not inconsiderable number of unsuspected carcinomas that are discovered on microscopic examination. If any question of completeness of the operation exists there is no hesitation to reoperate promptly at which time a total homolateral extirpation is carried out on the involved side and a search made for any evidence of spread.

In the presence of extracapsular invasion a radical unilateral neck dissection and total removal of the involved lobe are carried out.

In dealing with clinically obvious cancers (which may or may not have regional lymph node metastases) the patient is operated upon with the intention of radical gland removal combined with block dissection of the involved side.

When the lesion is considered inoperable as much of the neoplasm as possible is removed. Every effort is exerted to clean the trachea. Removal of such neoplastic masses may occasionally be facilitated by use of the electro-surgical unit.

While our attitude in regard to the treatment of thyroid carcinomas has been to consider them a surgical problem, irradiation therapy enters the picture when removal is incomplete or in the event of inoperability. When irradiation is used in most instances treatment is applied through two lateral fields treating one field a day alternating between the two fields. The usual dose amounts to about 3 000 roentgens (as measured in air) to each of the two fields. The radiation is usually given at the rate of 200 roentgens per day. Two hundred KV filtered radiation of HVL 1.0 mm Cu is used at a distance of 50 cm.²⁹

Before instituting irradiation therapy microscopic examination of at least a biopsy specimen is mandatory.

The possibility of postoperative respiratory obstruction occurring either following surgery or during the course of postoperative irradiation therapy must be kept in mind. Tracheotomy is strongly advised upon completion of the operation if there is the slightest doubt about the patient's breathing rather than waiting until cyanosis makes it mandatory. It is also recommended for patients judged inoperable in whom intensive postoperative irradiation therapy is contemplated, even though partial removal of the neoplastic mass leaves the trachea relatively free.

SUMMARY AND CONCLUSIONS

The incidence of malignancy in all surgically treated goiters during a 10 year period was 4.6 per cent (61 malignant neoplasms in 1,326 cases).

Of the 1,326 surgically treated goiters 1,033 (78 per cent) were in females and 293 (22 per cent) were in males.

Thyroid cancer was found in 48 females (79 per cent of the total) and in 13 males (21 per cent of the total) or a sex incidence of 4.64 and 4.44 per cent respectively.

The incidence of malignancy in individuals with clinically nodular goiters (considering both sexes and single as well as multiple nodules) was 6.94 per cent.

Among females with clinically nodular goiters the incidence of malignancy was 6.5 per cent, among males 9.1 per cent. Considering multinodular glands alone the incidence of malignancy for females was 6 per cent and for males 9.56 per cent. Considering glands with only a single nodule found on clinical examination the incidence of malignancy was 8.4 per cent among females and 7.14 per cent among males.

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In individuals having clinically diffuse palpable goiters the incidence of malignancy among the females was 4.5 per cent, again there were no cancers in the males of this group.

Thyroid nodules were frequently overlooked during clinical examination and occasionally described where subsequent examination by both the surgeon and the pathologist failed to confirm their presence.

Youth does not minimize the likelihood of thyroid malignancy.

The presence of hyperthyroidism in no way excludes or minimizes the possibility of malignancy. Clear cut hyperthyroidism was present in 26 per cent of the patients in this series.

While the immediate cause of thyroid malignancy remains obscure most if not all thyroid cancers seem to originate in adenomatous foci. In all but one of the patients in this series a history of previous goiter was elicited.

In patients with clinically palpable nodular goiters thiouracil (and similar compounds) should be used only as a preoperative measure primarily because of the high incidence of malignancy in such goiters and secondarily because the question has been raised that such drugs are in themselves carcinogens or may enhance cancer susceptibility.

There are no reliable signs and symptoms by which the diagnosis of early thyroid cancer may be established. In clinically suspicious lesions the presence of hoarseness and demonstrable vocal cord paralysis constitutes ominous supportive evidence of advanced neoplasia.

Frozen section examination at the time of operation is unreliable and occasionally misleading, and consequently should not influence the surgeon's judgment too seriously.

The classification of thyroid cancers likewise continues to vary in different centers although fortunately those most frequently adopted by others are characterized by increasing simplicity. Portmann's classification based on the amount of infiltrative growth affords a common denominator applicable to most of the popular classifications and thus allows a basis for comparative study.

In this series of 61 cancers 56 were classified as epithelial in origin and therefore carcinomas and 5 were identified as sarcomas in incidence of 91.8 and 8.2 per cent respectively.

All of the sarcomas were designated as spindle cell type. While this high incidence of sarcomatous lesions is open to question at least one of these cases offered strong supportive evidence of its sarcomatous nature in the form of not only hyaline change but also cartilage formation.

Whatever the true nature of these lesions might be the diagnosis of thyroid sarcoma offers categorically an extremely grave prognosis.

The prognosis for epithelial neoplasms is far better and in many instances quite optimistic.

Our attitude in regard to the treatment of thyroid carcinomas has been to consider them as surgical problems with irradiation therapy entering the picture when removal is complete or in the event of inoperability.

Our attitude in respect to nodular goiters has been to regard them as having sufficiently high malignant potentialities to be regarded as precancerous lesions. And since the operative mortality (excluding cancers) for thyroidectomy is merely 0.3 per cent we strongly urge thyroidectomy for all such patients unless serious contraindications exist.

REFERENCES

1. Batts, M. Jr. O teogenic Sarcoma of Thyroid Gland Report of Case Am J Surg 49 300-302 1940
2. Bielschowsky, F. Distant Tumors Produced by 2 Amino and 2 Acetyl amino fluorene, Brit J Exper Path 25 14 1944
3. Bielschowsky, F. Tumors of Thyroid Produced by 2 Acetyl amino fluorene and Allyl thiourea 25 90-95 1944
4. Beierwaltes, W. H. Thyrotoxicosis Remissions After Thiouracil Tr Am A Study Goiter, p 118-130 1942-46
5. Beierwaltes, W. H. and Sturgis, C. C. Complications Following Administration of Thiouracil Am J M Sc 212 517-522 1946
6. Brenner, A. G. and McKnight, P. B. True Adenomas of the Thyroid Gland and Their Relation to Cancer Tr Am A Study Goiter 176-190 1940
- Broders, A. C. and Larkhill, E. M. Symposium on Surgical Lesions of Thyroid Diffuse and Adenomatous Goiter and Goiter Induced by Various Agents SURGERY 16 633-646 1944
8. Cattell, R. B. More Optimistic Approach to Cancer of Thyroid West J Surg 54 444-449 1946
9. Clute, H. M. and Albright, H. L. Thyroid Adenomas and Their Clinical Complications With Especial Reference to Discrete Adenoma New England J Med 215 1049-1054 1936
10. Cole, W. H., Slaughter, D. P. and Rosater, L. J. Potential Dangers of Nontoxic Goiter J. A. M. A 127 883-888 1945
11. Cole, W. H., Ellett, W. H. and Womack, N. A. Production of Hyperplasia of Thyroid Gland by Chemical Means With Special Reference to Iodine Bases and Their Derivatives Arch. Surg 22 96-935 1931
12. Cole, W. H. Womack, N. A. and Gray, S. H. Thyroid Infections and Toxemias Pathological Changes in Human Gland Am J Surg 6 212-29 1933
13. Coller, F. A. The Inevitable Damage Consequent Upon Goiter Boston M & S J 193 545-550 1925
14. Coller, F. A. Adenoma and Cancer of Thyroid Study of Their Relation in 90 Epithelial Neoplasms of Thyroid J. A. M. A 92 457-462 1929
15. Coller, F. A. and Arn, R. D. Thyroidectomy for Goiter Without Hyperthyroidism 10 Operative Results in Adenomatous Goiters With Normal and Hypofunction West J Surg 39 501-506 1931
16. Coller, F. A. and Potter, E. B. End Results of Thyroidectomy Ann. Surg 94 565-581 1931
17. Cope, O. Rawson, R. W. and McArthur, J. W. Hyperfunctioning Single Adenoma of Thyroid Surg., Gynec & Obst 84 415-426 1947
18. Crile, G. Jr. Papillary Tumors of Thyroid and Lateral Aberrant Thyroid Origin, Surg. Gynec & Obst 69 39-47 1939
19. Crile, G. Jr. Discussion of Beierwaltes, p 125
20. Crile, G. Jr. Papillary Carcinoma of the Thyroid and Lateral Cervical Regions Surg., Gynec & Obst 85 75-86 1947
21. Crile, G. and Crile, G. Jr. Radical Operation for Malignant Tumors of Thyroid Gland Surg. Gynec & Obst 64 92-934 1937
22. Editorial. Thiourea and Experimental Carcinogenesis in the Thyroid J. A. M. A 127 27-29 1945
23. Foot, N. C. Pathology in Surgery Philadelphia 1945 J. I. Lippincott Co
24. Foster, H. L. Carcinoma of Thyroid Surg. Gynec & Obst 66 550-560 1938
25. Goetsch, E. A New Concept Regarding the Origin of So-called Primary Carcinoma of the Hyperplastic Gland Ann. Surg 118 43-55 1943
26. Graham, A. Malignant Tumors of Thyroid Epithelial Types Ann Surg 82 30-44 1935
27. Graham, A. Malignant Adenoma of Thyroid Local Recurrences in Veins of Neck Surg. Gynec & Obst 66 557-560 1938
28. Graham, A. The Development of the Thyroid and in Man Their Relation to Thyroid Tumors in Man Tr (Gland) Philadelphia 1936 J. I. Lippincott Co
29. Hertler, A. F. Lippincott Co

- 30 Hinton J M and Lord, J W Jr Is Surgery Indicated in All Cases of Nodular Goiter, Toxic and Nontoxic? J A M. A 129 605 606, 1945
- 31 Horn R C Jr Welty R F Brooks F P, Rhoads J E and Pendergast, E P Carcinoma of the Thyroid, Ann Surg 126 140 155 1947
- 32 Jovee T M Menne F R and Zeller W E Some Unusual Tumors of Cervical Region Arch Surg 42 375 370 1941
- 33 Kennedy R L J Carcinoma of Thyroid Gland in Children J Pediat 7 631 650 1935
- 34 Kennedy R I J Nodular Goiter Among Infants and Children Tr Am A Study Goiter p 223 1940
- 35 King W L M and Pemberton J deJ So Called Lateral Aberrant Thyroid Tumors Surg Gynec & Obst 74 931 1001, 1942
- 36 Kroger W L Spindle Cell Carcinoma of Thyroid, Tr West S A. (1941) 51 96 100 1942
- 37 Lahey F H and Ficarra B J The Lateral Aberrant Thyroid Surg Gynec. & Obst 82 705 711 1946
- 38 Lahey F H Hare H F, and Warren, S Carcinoma of Thyroid Ann Surg 112 977 1005 1940
- 39 Lamberton J deJ and Duck B M Symposium on Malignant Lesions of Thyroid Goiter in Children SURGERY 16 756 763 1941
- 40 Portmann U V Malignant Tumors of Thyroid Gland Surg Gynec. & Obst 70 185 192 1940
- 41 Pappel I D Telford C P and Curtis G M The Surgical Therapeutic Significance of the Functional Behavior (Radioiodine) of the Nodular and Parathyroid Thyroid Tissue of Patients With Toxic and Nontoxic Goiter Tr Am A Study Goiter p 175 204 1942 46
- 42 Rlenhoff W F Gross and Microscopic Structure of Thyroid Gland in Man Arch Surg 19 986 1036 1939
- 43 Ro h R and Raider I Radiation Therapy of Carcinoma of Thyroid, Radiology 44 556 564 1945
- 44 Simpson W M Primary Thyroid Carcinoma Simulating Hypernephroma Ann Clin Med 4 688 692 1936
- 45 Simpson W M Clinical and Pathological Study of 55 Malignant Neoplasms of Thyroid Gland Ann Clin. Med 4 643 667 1946
- 46 Simpson W M Thyroid Metastasis to Bones Existence of So called Benign England J Med 236 207 210 1947
- 47 Tark Surgical Treatment of Malignant Goiter
- 48 Tink
- 49 Vand
- 50 Warc
- 51 Weller G L Jr Development of the Parathyroid and Thymus Glands in Man Carnegie Cont to Emb 24 95 1933
- 52 Wilensky, A O and Kaufman P A Hurthle Cell Tumor of Thyroid Gland Surg Gynec & Obst 66 110 1938
- 53 Wilson R H DeEds F and Cox A J Jr Toxicity and Carcinogenic Activity of 2 Acetoaminofluorene Cancer Research 1 595 608 1941
- 54 Womack N A and Cole W H Normal and Pathologic Repair in Thyroid Gland Arch Surg 23 466 476 1931

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Book Reviews

Sterility and Impaired Fertility By Cedric Lane Roberts CVO, MSc, FRCS, FICOG
Gynecological Surgeon, Royal Northern Hospital London, and associates 1p 400
with many illustrations New York 1948, Paul B Hoeber, Inc

This is the second edition of a well known monograph dealing with human fertility. The authors are gynecologists from London and Glasgow an "andrologist," an assistant in a London fertility clinic and B L Wiesner, the distinguished biologist who has done so much work in the field of human reproduction. The book is designed for the general practitioner and has an attractive practical approach. It is nicely organized and surprisingly complete for a small monograph. The whole field of male and female infertility is covered and both clinical and laboratory approach, with practical and theoretical considerations are presented in detail. It is an authoritative presentation with little to which one can take exception. It is the kind of volume that one can easily use in the actual practical study and treatment of a clinical problem.

Altogether, it is at least as good a practical guide as is presently available and is to be recommended for such use.

Atlas of Roentgenographic Positions By Virginia Merrill while Educational Director Picker X-Ray Corporation, Ed 1 Cloth Two volumes 1p 708, over 1,500 illustrations
St Louis, 1949 the C V Mosby Company \$30

This Atlas represents a most complete assemblage of known roentgenographic positions in literature and is written for the student technician, or doctor desiring to obtain a comprehensive and fundamental knowledge of this field. The Atlas consists of two volumes of 408 page which include over 1,000 illustration. The first volume is comprised of sections dealing with preliminary steps in roentgenography general anatomy and anatomic terms upper extremity lower extremity shoulder girdle bone thorax pelvic girdle spinal column and a glossary of medical and anatomic terms. The second volume presents the skull sinuses cerebral pneumography facial bones mouth neck, body cavities thoracic viscera digestive system excretory system, and female reproductive system. At the end of each volume is an extensive bibliography of the material contained within if further study is desired.

The text is concise and well written. The printed material is large enough to be easily read and the illustrations of the positions used and the resultant roentgenograms are exceptionally clear and accurate. A helpful feature for the student and technician is the discussion and the line illustrations of the anatomy which precede each section.

This is highly recommended as an excellent reference book for all of the standard positions and almost all of the more unusual and specialized positions used in roentgenographic positioning.

Clinical Aspects and Treatment of Surgical Infections By Frank L. Meloney, MD
FACS Associate Professor of Clinical Surgery, College of Physicians and Surgeons Columbia University Associate Visiting Surgeon Presbyterian Hospital New York N Y Cloth 1p 840 with 284 illustrations Philadelphia, 1949 W B Saunders Company \$12

Recent advances in antibacterial therapy have greatly influenced the management of surgical infections. The sulfonamides and the antibiotics have made extensive surgical procedures safe that were previously impossible and they have modified the extent of surgery necessary in other conditions. This book presents a thorough review of the prin-

ciple of treatment of surgical infections emphasizing the changes in therapy brought about by the antibiotics. The management of surgical infections is discussed not only from the point of view of the anatomic changes present but particularly from the standpoint of directing specific therapy toward the removal of the etiologic agent.

The section discussing acute and chronic gangrene are of course, excellent. The review of the treatment of infected wounds is more complete than that available in any other single volume.

The literature is reviewed completely on each subject and many illustrated cases are presented.

The book provides an extensive discussion of the clinical uses of bacitracin developed in the author's laboratory. In his enthusiasm for this very valuable drug however the author fails to discuss the dangers of its parenteral administration.

While this volume is primarily a reference book it discusses from a practical point of view the problems of surgical infections that are frequently seen in clinical practice.

British Surgical Practice Under the general editorship of Sir Ernest Rock Carling, F.R.C.S., F.I.C.I. Consulting Surgeon Westminster Hospital and J. Patterson Ross, M.S., F.R.C.S. Surgeon and Director of Surgical Clinical Unit St. Bartholomew's Hospital Professor of Surgery University of London Vol. IV Cloth St. Louis, 1948 The C. V. Mosby Company \$15

Volume IV of this splendid series continues to be of the same type of character as the others. The illustrations are excellent and are profuse. The text is concise and well done. The chapter on fractures is particularly good as are the chapters on aspiration biopsy, which is excellently illustrated and on injuries of the hand. It is regretted however that in the consideration of herpes zoster the extremely simple and yet effective procedure of interrupting the sympathetic impulses with procaine is not discussed.

British Surgical Practice Under the general editorship of Sir Ernest Rock Carling, F.R.C.S., F.R.C.P. Consulting Surgeon Westminster Hospital and J. Patterson Ross, M.S., F.R.C.S. Surgeon and Director of Surgical Clinical Unit St. Bartholomew's Hospital Professor of Surgery University of London Vol. V Cloth St. Louis, 1948 The C. V. Mosby Company \$15

Volume V is the same type as the previous volumes of this system of surgery. It is well illustrated. A consideration of the various subjects from Hodgkin's disease to lymphogranuloma inguinale is done concisely and in a lucid manner. It is of interest to devote a chapter to tuberculous arthritis. In addition to the profuse number of excellent colored illustrations

which add materially to the value of the book.

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PROBLEMS IN THE DYNAMICS OF BLOOD FLOW

CONDITIONS CONTROLLING COLLATERAL CIRCULATION IN THE PRESENCE OF AN ARTERIOVENOUS FISTULA, FOLLOWING THE LIGATION OF AN ARTERY

EMILE HOLMAN, M.D., SAN FRANCISCO CALIF

(From the Laboratory for Surgical Research Stanford University Medical School)

CONTRIBUTIONS to medical literature may be the product of philosophic speculation or they may follow observations in the experimental laboratory from which logical and orderly deductions may be made. The first method has frequently resulted in conclusions wholly unsupported by reality, as for example the curious conceptions emanating from Galen's fertile imagination concerning the circulation of blood. Despite their illogical assumptions and their complete contravention of easily observed facts these phantasies of Galen were universally accepted for an unforgivable period.

Even today however the circulation of blood both in health and in disease presents many diverse problems awaiting proper solution. In the 1936 edition of Starling's *Principles of Human Physiology* a standard textbook by a great English physiologist appeared this statement: "The physical principles involved in the hydrodynamics of the circulation are of great complexity, and are for the most part as yet unsolved."

A particularly puzzling problem has been that of collateral circulation. In 1940 the late Sir Thomas Lewis¹ reviewed the subject and presented some provocative suggestions. With reference to the compensatory growth of collateral vessels around an arterial block and the growth of vessels distal to a simple arteriovenous fistula he wrote:

It seems clear that although the establishment of an arteriovenous fistula acting as a short circuit at first decreases the blood supply to the distal parts of the limb this state is not maintained. With passage of time the blood flow to the distal parts tends to become restored. *The recovery may in fact proceed to the point where there is actually greater flow than to the normal limb.* In

¹Presented in part as the Edward D. Churchill lecture before the Faculty for Surgical Club October 15, 1949 and as the presidential address at the third annual meeting of the Society for Vascular Surgery Atlantic City N. J., June 5, 1949.

emphasizing the powerful stimulus which the fistula provides for the development of the collateral channels, Reid² says that when we consider that the parts peripheral to a fistula are deprived of their allotted blood supply by reason of the hunt there is little wonder that nature makes a prodigious effort to compensate by collateral channels

When a main artery to a limb becomes blocked certain factors come into play, at once or after very short delay and tend to restore the circulation to the distal tissue. As Ricklinghaus³ pointed out there is as the result of the obstruction, a little rise of pressure proximal to it while there is a decided fall of pressure in the artery and its branches distal to it. These immediate changes in pressure increase the flow in branches issuing from the main artery proximal to the obstruction and supplying the territory in which the pressure is lowered.
 Macdonald⁴ has also pointed out that the increase in flow in the main artery proximal to the obstruction is not sufficient to explain the development of collateral channels.

amount of blood flowing through them might be held adequately to explain the development of collateral channels when the main artery of a limb is obstructed. It might be held to explain the well recognized increase in size of the main artery leading to an arteriovenous anastomosis. But it will not explain what is here reported namely an increase in the size of arterial channels very distal to a simple fistula for the fall in arterial and rise in venous pressure which are the necessary consequences of the original lesion must tend primarily to retard rather than to increase blood flow in these channels.

It is clear that hydrostatic factors provide no common basis to explain the compensatory growth of collateral vessels around an arterial block and the growth of vessels distal to a simple arteriovenous fistula. Searching for a common factor we find ourselves returning to Reid's generalization that the arterial channels develop to meet the needs of tissue deprived in part of blood supply. Chief interest lies in enquiring how this can come about. Neither adjustment of nervous control, nor a direct response of the affected vessels to increased pressure or nutrition can be regarded as a satisfactory explanation and we are brought to ask if arterial growth is not directly controlled by a stimulant a chemical stimulant arising locally as a product of the tissue need and acting locally. The growth of collateral channel is so locally adjusted and occurs under such different circumstances of pressure and flow that it now seems quite necessary to formulate an intimate and special mechanism to explain this permanent increase in size.

The essence of the matter seems to be that there is a local call by tissues in need and that to this call there is a local and adequate response.

Lewis' views are a direct challenge to the purely mechanistic theory which had been presented to explain the various phenomena surrounding an arterio

Evidence supporting this view has been presented in previous publications. Experiments were recorded which demonstrated that in the presence of a long

standing fistula the heart and the entire fistulous circuit including the fistula and the artery and vein between the fistula and the heart, became insidiously and progressively dilated* Concomitant with this dilatation there occurred a gradual increase in total blood volume When conditions at the fistula were altered as by ligating the artery just proximal to the fistula the artery distal to the fistula became dilated* This was demonstrated to be due to the increased volume of blood directed into it through a large collateral bed around and distal to the fistula (Fig 1) This truly remarkable opening up of large collateral vessels was interpreted as a direct response to the lowered peripheral resistance at the site of the fistula Additional evidence is now available which supports this view and which proves again the vulnerable character of armchair philosophizing when unsupported by experimental verification

Studies were first directed toward determining what happens to the arteries proximal and distal to a fistula immediately after its introduction into the arterial tree

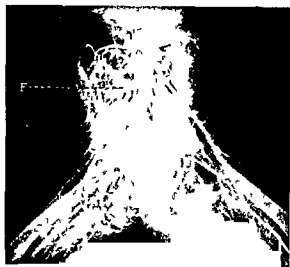
A 12.5 kilogram dog was anesthetized with pentothal the abdominal aorta was exposed and 24 c.c. of Thorotrast injected rapidly through a No 18 needle During the injection of the last few cubic centimeters roentgenograms of the pelvic and lower extremities were taken in rapid succession (Fig 2 a) A left femoral fistula 2 cm long was then established between the femoral artery and vein Immediate Thorotrast and subsequent bismuth oxychloride injection both revealed a definite reduction in the caliber of the arteries proximal and distal to the fistula (Fig 2, b)

This narrowing of the arteries is comparable with the reduction in the size of the heart which followed the opening of these newly formed fistulas and which is attributed to the deflection through the fistulas of a considerable volume of blood from the arterial into the capacious venous system The immediate intravenous infusion of 500 c.c. of salt solution restored the hearts to their normal size (Figs 3 and 4)

Having demonstrated that the first effect of opening an arteriovenous fistula is a contraction or narrowing of the artery proximal and distal to a fistula the Lewis theory that subsequent arterial dilatation is due to a chemical stimulant from ischemic tissues was subjected to the following experimental studies

Animal Amp 3 (18 kilograms) On March 28 1947 a high left thigh amputation was performed On April 11 1947 a 2 cm sized left femoral fistula was established On January 1948 nine months later the animal was killed and the aorta was injected with 1 per cent bismuth oxychloride suspension in 10 per cent gum acacia Before injection the fistula was isolated by ligation of the artery and vein proximal and distal to the fistula thus insuring that the injection mass would enter only the arterial bed and not the venous bed Marked dilatation of the femoral artery proximal to the fistula was disclosed with a definite though small increase in the collateral arterial bed (Fig 5)

Animal Amp 5 (19 kilograms) On Nov 11 1947 a left thigh amputation was performed On Dec 4 1947 a 2 cm sized fistula was established between the left femoral artery and vein On June 21 1948 roentgenograms revealed a moderate enlargement of the heart and it was noted that when the fistula was closed by digital pressure the pulse dropped from 90 to 70 definite evidence of an increase in total blood volume On June



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Fig 1—Great development of collateral vessels around and distal to an experimental iliac arteriovenous fistula at *F* to which blood had access only through the artery distal to the fistula, the proximal artery having been ligated. Note dilatation of vessels both proximal and distal to fistula.



a



b

Fig 2—*a* Normal arterial bed beyond the aorta as revealed by Thorotrast injection.

b The same arterial bed immediately after opening a femoral arteriovenous fistula at *F* resulting in a marked narrowing of the artery both proximal and distal to the fistula. Segment *P* should be compared with segment *P'* and segment *D* with *D'*.



Fig. 4 (III) — Mark I. Luer in left side occurs immediately following the opening of the right anterior neck fistula which was
performed by the infusion of 100 cc of saline solution
a) before Luer in left femoral fistula b) immediately after opening fistula c) after infusion of 200 cc normal salt solution

30, 1948, the animal was killed, and the thoracic aorta was injected with barium oxychloride. Roentgenograms showed a dilatation of the artery proximal to the fistula but surprisingly little if any, dilatation of the collateral bed in the vicinity of the fistula (Fig. 6).

Animal Amp 6 (29 kilograms). On Dec 12 1947, a high left thigh amputation was performed. On Jan 1st, 1948 an arteriovenous fistula 2 cm long was established between the left femoral artery and vein just below Poupart's ligament. A loud murmur was heard

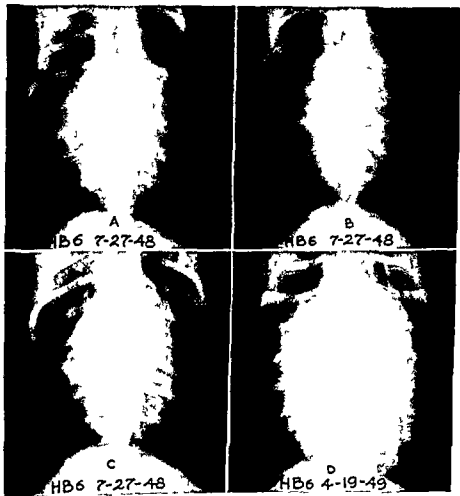


Fig. 4 (HB) — The first effect of opening bilateral fistulas was to decrease the size of the heart (B) which was promptly restored to normal (C) by infusion of salt solution followed by gradual dilatation as shown in roentgenogram (D) taken nine months later.

and an intense thrill was felt over the fistula during the first few weeks which then gradually subsided until it disappeared completely presumably due to closure of the fistula. Accordingly on May 13 1948 a second fistula 1.5 cm long was established between the left iliac vessels. The disappearance of the thrill and bruit incident to the femoral fistula was found to have been due to thrombosis of the vein at the site of the fistula, though the

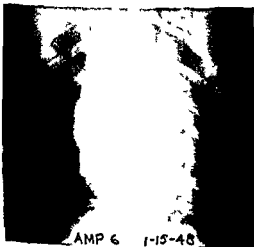


Fig 5

Fig 6

Fig 5 (A & B) — The production of a femoral artery-venous fistula on the side of a the artery proximal to the small branch of

animal failed to evoke branches in the small proximal artery 1



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Fig 7 a and b (Amp 6) — The production of a femoral fistula in an animal previously subjected to a thigh amputation was followed by the usual cardiac dilatation.

artery itself was patent. Again a loud continuous murmur was heard over the left inguinal area which persisted until the animal was killed one year later on May 9 1949. Before death, roentgenograms of the heart showed a considerable increase in its size (Fig 7). The femoral and iliac vessels were isolated. It was easily demonstrated that the terminal femoral artery beyond the fistula with a diameter of 3 mm was pulsating vigorously and that the flow in it was directed cephalad, carrying blood into the fistula from below. Manometric readings in the artery distal to the fistula revealed a pressure of 42 mm Hg when the

(the fistula)
Pressure
distal to the fistula
open

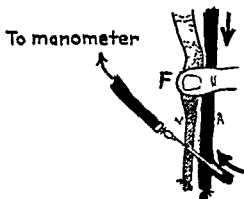


Fig 5 (Amp 6)—Closure of an iliac fistula established on the side of a previous iliac amputation produced a marked elevation in blood pressure in the artery distal to the fistula indicating that the blood flow from a very extensive collateral bed (see Fig 3) was directed cephalad through this artery into the fistula.

— 1 — + 94 open but rose precipitately to 108 mm Hg when the fistula of

fistula was 110 mm Hg with the fistula open and rose to 132 mm. Hg on closing the fistula distal to it. Following these studies the animal was killed the thoracic aorta was cannulated, and bismuth oxychloride was injected for the radiographic visualization of the arterial tree below the trifurcation of the aorta (Fig 9)

The extraordinary collateral bed in Animal Amp 6 which poured blood into the fistula by *reversed or cephalad flow of blood through the artery distal to the fistula*, and which developed despite amputation of the leg beyond the fistula, gave positive proof that ischemic tissues are unnecessary for the development of abundant collateral vessels



Amp 6
Amputation Dec 12/48
Femoral Fistula Jan 15/49
Iliac Fistula May 13/49
Injection May 10/49

Fig 9 a and b -
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The difference in degree of collateral circulation manifested in Animals Amp 3 and Amp 6 provided evidence also that the extent of collateral development is dependent in part upon the duration of the fistula. If the Lewis theory were correct that a chemical substance produced in ischemic tissues excites the development of collateral vessels it would be logical to assume that once an adequate flow to an extremity had been established there would be no further production of such a chemical substance and therefore no further increase in collateral circulation. This is contrary to fact. For example examination of the collateral beds in Animals T10 and T24 (Fig 10) indicates that the develop-

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as the femoral fistula in T24 which had been present for six and one half years produced a truly remarkable collateral bed with great

dilatation of the main artery and all its branches proximal and distal to the fistula, all of which poured blood into the venous system and back to the heart by way of the fistula

Clinical evidence is also overwhelming that this development of collateral circulation goes well beyond the necessity envisioned by Lewis of providing an adequate circulation to tissues deprived of blood as time goes on in the presence of an arteriovenous fistula the leg may become progressively larger than its



follow the affected leg in a growing child may become longer through greater growth of either femur or tibia, the surface temperatures on the side of the fistula may become higher by 2 to 3 degrees and the volume of blood flowing to the aff

dilatation

These effi described in literature which have shown puzzling variations from those just mentioned as for example atrophy of a limb beyond a fistula or a limb colder distal to the fistula than the normal limb ¹²

The failure of collateral vessels to develop in Animal Amp 5 in contrast with the great development of collateral vessels in Animal Amp 6 provided the first evidence that the most important condition necessary for the opening up of collateral vessels is that the artery *distal* to the fistula be patent and that it have large branches through which blood may find access to the area of lowered resistance introduced by the fistula. In a previous publication⁷ the opinion had been expressed that the effects of an arteriovenous fistula upon the circulation depended upon what happened fortuitously to the vessels proximal and distal to a fistula during the healing process that unyielding fibrous tissues deposited around one or another of these vessels might prevent their usual dilatation and therefore inhibit or alter the expected effects of an arteriovenous fistula. It was asserted also that heavy scarring around the fistula itself might prevent the progressive enlargement of the fistula and thus prevent the progressive effects of the fistula upon circulation. In order to verify or disprove these contentions a number of different experiments were undertaken.

Bilateral femoral fistulas were established each located in exactly the same place just distal to the emergence of the deep femoral branch in an area where usually no branches are encountered. The fistulas in all experiments were made exactly 2 cm. long and great care was taken to include only a minimal amount of the wall of the artery and vein in the anastomosing stitch and above all to avoid any constriction or stenosis of the artery or vein at either end of the fistula. The fistulas were made 2 cm. long first to insure their remaining patent (small fistulas heal spontaneously) and second to get their effect promptly that is over one year's time rather than waiting ten to twenty years as in clinical subjects. Conditions at the site of one or the other of the two fistulas were then altered (1) by applying an aluminum band encircling but not constricting the artery proximal to the fistula (Animals HB₁ and HB₂) (2) by applying a band to the artery distal to the fistula constricting it to one half its diameter (Animals HB₃ and HB₄) (3) by applying a band on the vein just proximal to the fistula (Animals HB₅ and HB₆) (4) by ligating the artery just distal to the fistula on one side, and just distal to the first branch beyond the fistula on the other side (Animals HB₇ and HB₈) (5) by doubly ligating and dividing the femoral artery on one side and producing a fistula on the other side (Animal HB₉).

Startling and important information was obtained in these animals as the following protocols will disclose

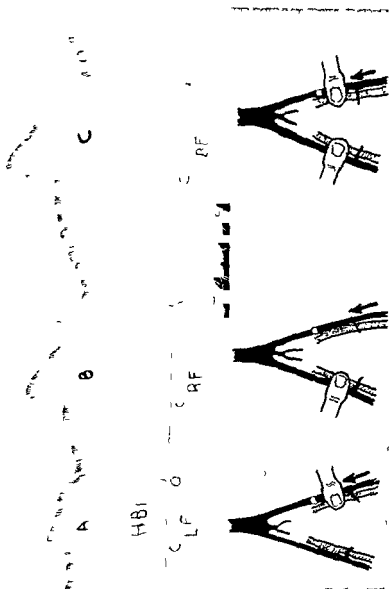


Fig. 11 (HB) — Kymographic record of carotid pressure depending upon tensioning at site of late arterial fistula. A. On closure of left fistula which had been modified by band encircling artery proximal to the fistula the carotid pressure rose moderately. B. On closure of right fistula, unmodified by band, produced a much more pronounced effect on carotid pressure. The extent of rise in B is of the same order as in A. C. Simultaneous closure of both fistulas produced a very pronounced elevation of blood flow through the fistulas into the venous bed.

Animal HB₁ (18 kilograms) Bilateral fistulas were established on March 4, 1948 an aluminum band being applied to the artery just proximal to the fistula on the left. Within twenty-four hours the right leg showed some edema the left none. Forty-eight hours later the edema on the right had become marked the left leg being still without swelling. By March 9 the edema began to subside, but as it subsided the superficial veins became prominent. By April 16 the swelling on the right had completely subsided and the superficial veins were markedly prominent as compared to the left, indicating a greater flow through the right fistula and a greater venous pressure distal to the right fistula. The disappearance of the edema concomitant with the appearance of dilated veins coincides, it is believed, with the dilatation of the veins proximal to the fistula to a size sufficient to provide adequate venous return for the increased arterial flow to the limb, thereby diminishing the pressure in the venous bed distal to the fistula.

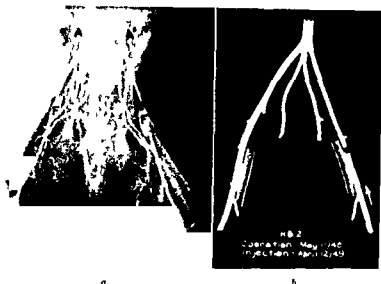
On April 5, 1949, one year later the veins on the right were very prominent as compared with the left and the thrill and bruit were much more intense on the right. With both fistulas open the pulse rate was 132. On closing the left fistula the pulse dropped to 114. On closing the right fistula it dropped to 88. On closing both fistulas it dropped to 84. The greater reduction in pulse rate on closing the right fistula was additional evidence of a greater flow of blood through the fistula on the right as compared with the left. Under nembutal anesthesia the venous pressure in the left jugular vein was 5.5 cm. of water in the superficial veins of the right lower leg 41 cm. of water and in the left leg 19.5 cm. of water, further evidence of a greater flow through the fistula on the right.

The two fistulas were isolated and kymographic readings of pressures in the left carotid artery were obtained under varying conditions at the site of the fistula (Fig. 11). Following ligation of the artery and vein proximal and distal to the fistulas the arterial tree was visualized by roentgenograms taken after the injection into the thoracic aorta of bismuth oxochloride. A good collateral bed was demonstrated on both sides with some dilatation of the artery proximal to the fistula on the right as compared to the normal sized artery on the left, this normal size being due to the band on the artery proximal to the fistula which prevented its dilatation by limiting the volume flow of blood through it. It is very significant that the collateral bed around the fistula was much more extensive than that observed in those animals in which the artery distal to the fistula was ligated as in HB and HB or ligated as in HB and HB.

Animal HB (Duplicate of HB₁) The fistulas were established on March 11, 1948 with a band encircling but not constricting the artery proximal to the fistula on the left. Again as in HB₁, a marked edema of the right leg appeared within twenty-four hours but none on the left. On March 16 the edema had subsided and the superficial veins on the right were very large prominent veins on the left.

On April 6, 1949 the thrill and bruit were much more intense on the right. Closure of the fistula on the left by digital pressure caused a retardation in pulse rate from 116 to 104. Closure of the fistula on the right slowed the pulse from 124 to 88. This is evidence of a greater flow through the fistula on the right as compared with the left. Under intravenous nembutal anesthesia venous pressure in the right jugular vein was 8 cm. water in the veins of the right lower leg below the fistula 23 cm. water and in the left lower leg 21.5 cm. water. Both fistulas were isolated followed by visualization of the arterial tree (Fig. 12) which revealed a good collateral bed in the thigh on both sides. Dilatation of the artery proximal to the fistula on the right but absent on the left and large patent arteries distal to the fistula on both sides.

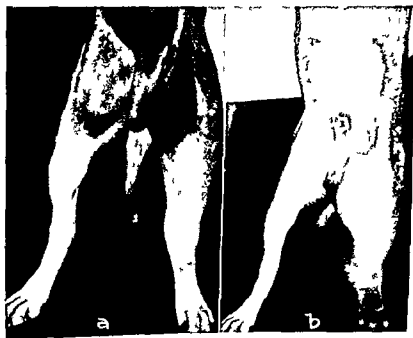
Animal HB₂ (14.4 kilogram) Two fistulas were established on April 7, 1948. On the right aluminum bands were applied encircling the vein both proximal and distal to the fistula but not constricting it. On the left an aluminum band was applied encircling the vein proximal to the fistula but not constricting it. Marked swelling of the left leg appeared promptly within six hours following operation. The next morning the animal was found dead, both legs markedly swollen. Both anastomoses were intact, there was no hemorrhage, the heart was small and contracted. It was obvious that the animal died of



a

b

Fig 12 a and b (IIB) —Visualization of arterial bed in IIB revealed a good collateral bed on both sides and dilatation of artery proximal to fistula on right but no dilatation of proximal artery on left due to modifying effect of encircling band on proximal artery which restricted the amount of blood flowing through this artery (Compare arteries A and A')

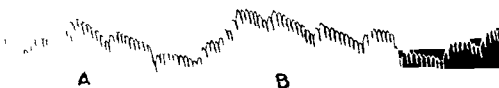


a

b

flow of blood into both legs by deflection of the arterial flow into the distal veins from which blood could not easily return to the heart due to the encircling bands on both femoral veins proximal to the fistula.

Animal HB (2.2 kilograms) A 2 cm sized fistula was established on the left with an aluminum band encircling the proximal vein but not constricting it. No fistula was produced on the right. Immediately after opening the fistula the pulse rate increased to 122 and respirations to 120. This strain on the animal's circulatory system was only temporary however, and on the following day the pulse rate had slowed to 160. Within



HB 4 Carotid Pressure

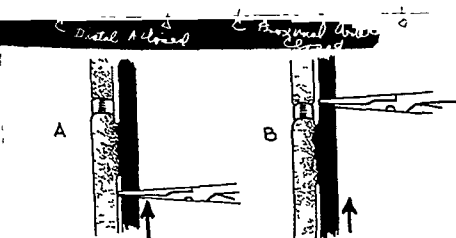


FIG. 14 (HB).—4. Closure of artery distal to fistula produced a rise in carotid pressure only slightly less than the blood pressure rise on closing the artery proximal to the fistula (B) indicating a considerable retrograde flow into the fistula through the distal artery.

twenty-four hours a remarkable swelling of the leg appeared and gradually grew to elephantiasis proportion never to regress (Fig. 13). The pulse rate remained greatly accelerated on July 11 the rate with the fistula open was 120 and 120 with it closed. By May 13, 1949 the swelling of the leg had become extreme accompanied by marked thickening of skin and an induration of the subcutaneous tissue quite like that of a true elephantiasis which it greatly resembled. The pulse rate was 124 with the fistula open 104 with it closed. End intravenous nembutal anesthesia venous pressure in the normal

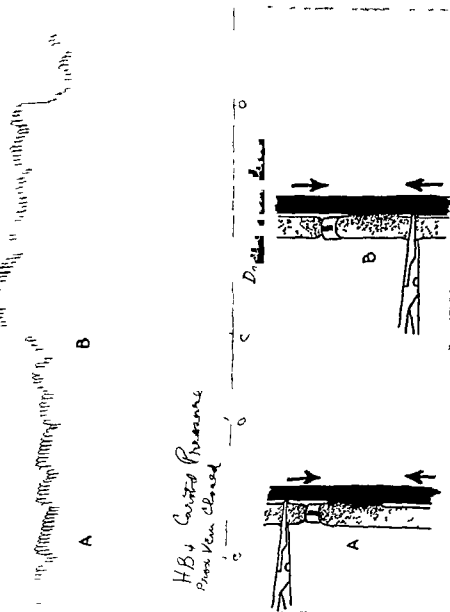


Fig 15 (HB) — Closure of proximal vein did not affect carotid pressure in the least. Indicating complete closure of vein at site of band as proved by subcutaneous pressure. Closure of distal vein into which both proximal and distal arteries pass produced a complete closure of the artery at the point of closure of the distal vein. This

right lower leg was 19 cm water, which did not change on opening or closing the fistula. The pressure in the left jugular vein was 5 cm water, which also did not change on closing the fistula. The venous pressure in the left thigh was 32 cm water with the fistula open and 35 cm with the fistula closed. The fistula was isolated and kymographic records of carotid pressure were made under varying conditions at the site of the fistula (Figs 14 and 15).

An important demonstration was the retrograde or cephalad flow of blood in the artery distal to the fistula. For example closure of the fistula produced a rise in blood pressure in the cannulized artery distal to the fistula. Subsequent visualization of the arterial tree (Fig 16) revealed an extraordinary collateral bed bringing blood to the fistula by cephalad flow of blood through the dilated artery distal to the fistula.

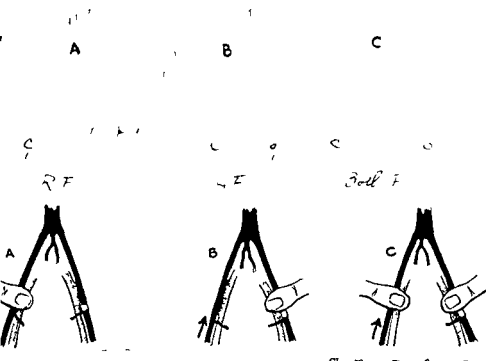


Fig 16 (HR4) — Demonstration of remarkable collateral bed around and distal to fistula on left with dilatation of artery both proximal and distal to fistula. Flow in distal artery was cephalad. Note dilatation of artery well beyond the fistula below the knee as compared with the normal arterial bed on right. (Compare arteries A and A' B and B' C and C').

Animal HB (28 kilograms) On July 23 1948 bilateral fistulas were established but on the left an aluminum band was applied to one half its normal diameter to the fistula on the right. On April 18 1949, the pulse digital pressure it was 100 mm of blood through the right fistula. Under nembutal anesthesia kymographic records of carotid pressures under varying conditions at the fistula indicated clearly that the flow of blood in the artery distal to the right fistula was in the cephalad direction bringing blood to the fistula through a very well developed collateral bed as disclosed by the roentgen visualization of the arterial bed when injected with barium oxychloride.

Animal HB (17 kilograms) Bilateral fistulas were produced on July 27 1948 the left fistula being modified as in HB by an aluminum band compressing the artery distal to the fistula to one half its normal diameter. Within twenty four hours there was marked

swelling of the right leg only slight swelling of the left leg. By August 3 the swelling on the left had partially receded that on the right was still extreme, but by August 25 the swelling of both legs had receded remarkably, concomitant with the appearance of large prominent superficial veins. On April 19 1949, under nembutal anesthesia the two fistulas were isolated and arterial carotid pressures were recorded (Figs 17 and 18). Again retrograde flow through the artery distal to the right fistula was demonstrated and the



injected arterial tree revealed a marked collateral bed (Fig 19) around and distal to the fistula, which poured blood into the fistula by way of the distal artery. There was no such collateral bed on the left where the artery distal to the fistula had been constricted to one half its diameter.

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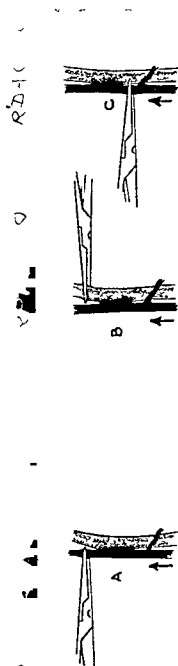


Fig. 18 (III) - 1. Closure of artery proximal to right fistula, produce increase of pressure in the artery proximal to the fistula, and also closure of right artery and vein. B indicates that if the artery is closed, it produces the circulatory disturbance of an arterial fistula. C, right distal artery, also produces if it is in pressure providing clear evidence of retrograde flow into fistula through the artery distal to fistula.

the artery. On the left the artery was ligated just beyond the fistula there being no such branch between the fistula and the ligature. On April 28, 1949, closing the right fistula retarded the pulse from 120 to 104 and closing the left fistula lowered the pulse from 116 to 100. Under nembutal anesthesia the venous pressure in the right lower leg was 33 cm. water, in the left lower leg 29.5 cm. water in the left jugular vein 35 cm. water.

Kymographic recordings of carotid pressure gave evidence that a greater flow of blood was passing through the right fistula than through the left fistula (Fig. 20) due no doubt to the additional flow of blood into the fistula by way of the one lone branch lying between the fistula and the ligature on the distal artery.

The paucity of collateral vessels around and below the fistulas on both sides as disclosed by roentgen visualization of the arterial tree was very striking (Fig. 21). When compared with the collateral circulation around fistulas unmodified by ligatures on the distal artery, this minimal development of collateral circulation may be directly attributed to interference with access to the fistula by way of the distal artery.

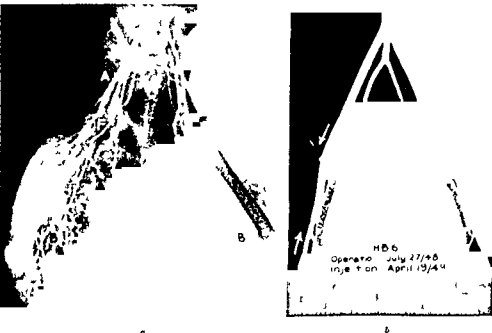


Fig. 19 a and b (HBs) —Remarkable collateral bed around and distal to unmodified right and left fistulas. The dilated branch between the left fistula and the ligature.

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Animal HB₆ (16 kilograms). On Dec. 7, 1948, bilateral femoral fistulas were established modified as follows. On the left the artery distal to the fistula was ligated just distal to the first branch. On the right the artery was ligated just beyond the fistula. On May 3, 1949, under intravenous nembutal anesthesia the two fistulas were isolated and carotid pressures recorded under varying conditions at the fistula. It was observed that the large branch between the fistula and the ligature on the right had become dilated to the point of being a direct flow through this

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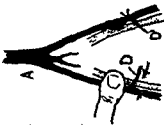
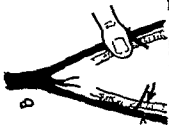
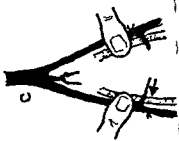


Fig. 6 (1933).—A. Closure of fistula on right modified by ligation of distal artery beyond the first large branch B produced a greater increase in blood pressure than (B). Closure of fistula on left modified by ligation of distal artery just beyond fistula and proximal to branch D. This is evidence of greater flow through the right fistula and is undoubtedly the result of cephalad flow through branch B which delivered blood to the fistula from the arterial bed. C. Closure of both fistulas simultaneously produced a greater rise in flow rate than closure of either fistula alone.

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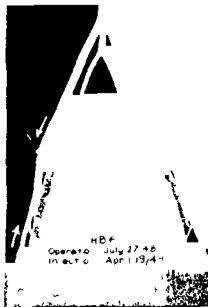
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Further evidence of this cephalad flow was the continuance of the thrill at the site of the right fistula when the artery and vein proximal to the fistula were ligated. Only on ligating the artery and the dilated branch distal to the fistula was this bruit and thrill controlled, indicating a substantial flow of blood into the fistula through the artery distal to the fistula. Visualization of the arterial bed revealed again a real paucity, almost complete absence, of collateral vessels around and distal to the fistula on both sides.

Animal HB (12.5 kilograms) On Aug 31, 1948, a single unilateral 2 cm fistula was produced between the femoral vessels on the left. On the right at the corresponding site two ligatures were applied to the femoral artery and the vessel divided between them. On Sept 7, 1948, the left leg was greatly swollen, whereas the right leg looked normal. This swelling persisted with the appearance of prominent superficial veins. On April 12, 1949 the animal was found dead after a fight. The arterial tree was injected and roentgenograms (Fig 22) revealed almost no collateral vessels on the side of the completely divided femoral artery but a truly remarkable enlargement of the collateral vessels around and distal to the left femoral fistula.

SUMMARY OF EXPERIMENTAL OBSERVATIONS

On opening a femoral fistula the artery both proximal and distal to the fistula became narrowed and its caliber definitely reduced in size, a phenomenon comparable with the reduction in size of the heart that accompanied the opening of the bilateral fistulas.

The production of an arteriovenous fistula in the main vessels of the stump of a limb previously amputated in the thigh resulted in dilatation of the artery proximal to the fistula and in the development of varying degrees of collateral circulation. If the fistula was located at the terminus of the artery or if there were no branches between the fistula and the ligated end of the artery, no increase in collateral circulation was observed. If one or more branches lay between the end of the artery and the fistula permitting access to the site of lessened resistance by retrograde flow through these distal branches extensive collateral circulation developed. Since potentially ischemic tissues beyond the fistula had been removed by amputation this development of collateral vessels could not be attributed to a chemical stimulant, as postulated by Lewis nor to tissue needs as suggested by Reid.

The effects of a fistula of standard length upon the circulation around it were greatly altered by altering the conditions at the fistulas. The application of a band encircling the artery proximal to the fistula prevented its usual dilatation due to limitation of the volume flow of blood through it.

Ligation of the artery distal to the fistula prevented the opening up of the collateral vessels by blocking easy access to the site of low resistance introduced by the fistula. If a small branch lay between the fistula and the ligature closing the distal artery this branch became dilated and by retrograde flow through it supplied the fistula with blood.

A large fistula without constriction of either the proximal or distal arteries provided the most effective stimulus for the dilatation of the artery proximal to the fistula and for the opening up of collateral vessels. The extent of collateral circulation was dependent upon the duration of the fistula.

If a band was applied to the vein proximal to the fistula thus blocking the easy return flow to the heart, the arterial flow was directed through the fistula into the distal vein producing a progressive edema of elephantiasis proportions.

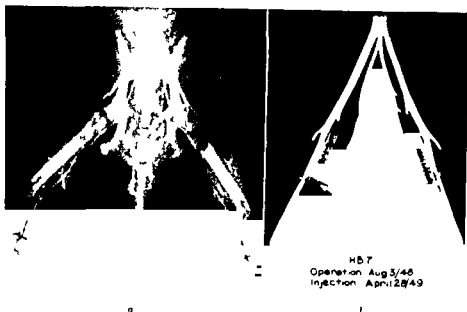


Fig. 1. a and b (HB) —Visualization of arterial bed in the presence of bilateral femoral fistulas modified by ligation of the artery distal to the fistula revealed a real dearth of collateral vessels as a result of these ligation which denied flowing blood access to the fistula by way of these distal arteries.



Fig. 2. a and b (HB) —Ligation and division of femoral artery on right resulted in minimal development of collateral vessels but introduction of femoral fistula on left produced a marked dilatation of proximal artery and development of an extensive collateral bed around and distal to fistula.

arterial pressure in the left subclavian artery was found to have dropped to 110 mm Hg, but rose to 142 mm Hg on closing the aorta beyond the subclavian artery a rise of 32 mm Hg. In the intact chest the pressure in the subclavian artery would have risen even higher on closure of the aorta.

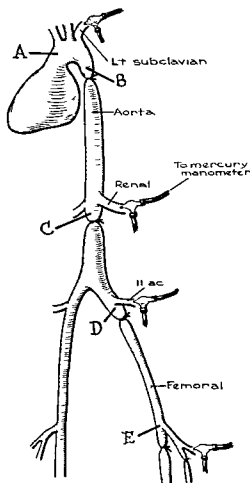


Fig. 23.—Arterial end pressure at any point in the arterial tree is dependent upon the peripheral resistance beyond that point that is the peripheral resistance at A is greater than at B. Hence end pressure at A must also be greater than at B. End pressures at C and D following ligation of artery are recorded in Fig. 24.

The extraordinary dilatation of the subclavian artery and the concomitant great increase in arterial pressure in this artery seen in the presence of aortic coarctation provides the best clinical evidence of the differing effects upon pressure produced by closure of a large artery close to the heart, as compared for example with closure of the terminal aorta or the smaller iliac artery.

Reduced to its simplest terms the effects of ligation of an artery may be described as follows. When the arterial segment *AB* (Fig. 23) is ligated at *Z*, the high end pressure at *Z* is promptly converted into high lateral pressure

When the vein proximal to the fistula was widely patent the edema which immediately followed the production of a fistula subsided concomitantly with the appearance of large and prominent superficial veins harboring greatly increased venous pressure. The disappearance of the edema was attributed to the dilatation of the main venous channels proximal to the fistula to a size which permitted draining off promptly the increased arterial flow attracted to the extremity in which the fistula lay.

Ligation and division of the femoral artery in one limb produced a minimal collateral circulation beyond the ligation as compared with an extraordinary enlargement of the arterial collateral bed in the other limb containing a femoral arteriovenous fistula, indicating that blood in the aorta was deflected more readily into the limb of lessened resistance due to the fistula than into the limb in which peripheral resistance had been increased by ligation of its main artery.

COLLATERAL CIRCULATION INCIDENT TO ARTERIAL LIGATION

In considering the various factors involved in determining the effects of simple arterial ligation upon the development of collateral circulation I should like to emphasize the postulate that blood pressure in the main arterial tree decreases as one approaches the periphery, that "lateral" pressure and "end" pressure in the large main vessels differ materially, that "end" pressure in the ascending aorta for example is very much greater than "end" pressure in the femoral artery. Lateral pressure at a given point in a main vessel is concerned with the pressure of the flowing blood obtained in a branch of the main arterial tree at that point and actually is the end pressure in that much smaller branch. *End pressure at a given point in a large artery is that pressure produced in the artery when the forward thrust of the flowing blood is suddenly blocked at that point by ligation.* It is obvious that end pressure at a given point in the arterial tree must be great enough to overcome the peripheral resistance beyond this point and that the sum total of resistance at *A* (Fig 23) just beyond the aortic valves is much greater than the resistance beyond the femoral artery at *D*. Since pressure must equal resistance to effect a flow of blood a greater pressure is required at point *A* than at point *D*. This greater pressure is effected largely by velocity of flow at *A* in terms of cubic centimeters per second which in turn depends upon the cardiac output, the total blood volume and the cross section of the artery at that point.

When an artery is ligated end pressure is suddenly converted into lateral pressure and the magnitude of this conversion has been found by experiment to depend entirely upon the location of the ligation in the arterial tree. For example, the mean arterial pressure of a branch of the common iliac artery was found to be 160 mm Hg (Fig 24). On closing the artery beyond the cannulized branch as well as the other two branches of the trifurcation of the aorta the mean pressure rose only 4 mm to 164 mm Hg. After opening the abdomen with a resulting mild fall in blood pressure the mean arterial pressure in the
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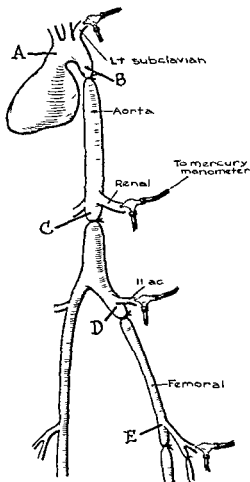


Fig. 3—Arterial end pressure at any point in the arterial tree is dependent upon the peripheral resistance beyond that point that is the peripheral resistance at A is greater than at D. Hence end pressure at A must also be greater than at D. End pressures at B, C, and D following ligation of artery are recorded in Fig. 24.

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primarily because the large volume of blood formerly flowing past *Z* is now forced into branch 1 which is much smaller than the parent artery. As a consequence, pressure in branch 1 and in the arteriolar and capillary bed *C* is raised greatly, whereas pressure in artery *A'* and in the arteriolar and capillary bed *C'* supplied by it has fallen greatly. The arteriolar bed *C'* being the only low pressure area blood from bed *C* will flow into bed *C'* and thence into *Y*. The cut between the two capillary beds

Similar conditions prevail when an arteriovenous fistula is introduced into the segment *XY* (Fig. 26), resulting in a great reduction in pressure in the arteriolar and capillary bed *C'* due to the easy flow and escape of blood through the fistula into the vein where resistance is low as compared with the much greater resistance to flow in the capillary bed distal to the fistula. Due to this low pressure area in bed *C'* blood will be attracted to it from the arteriolar bed *C* resulting in an increased flow through the corresponding collateral vessels which open up and become dilated in response to this increased flow.

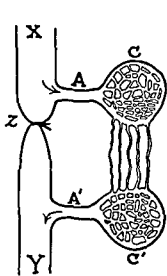


Fig. 25 - See text

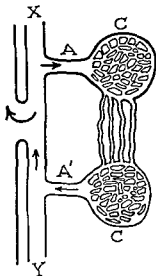


Fig. 26 - See text.

With full appreciation of these changes in pressure both around a ligated artery and around an arteriovenous fistula there is little need of postulating a chemical stimulant to open up the anastomotic or collateral bed.

Furthermore if we accept the premise that the end pressure in an artery depends upon the size of the artery and upon its location in the main arterial tree a number of phenomena are more easily understood as for example Halsted's dictum that the nearer to the heart an artery is ligated the less danger there is of gangrene; that is the higher the end pressure in an artery the higher becomes the lateral pressure on its ligation and the greater is the distending force available to open up anastomotic channels.

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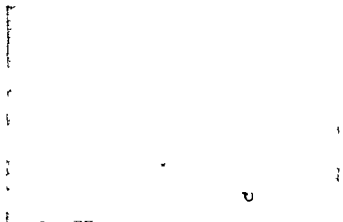


Fig. 4.—a Arterial pressure in branch of common iliac artery was very lightly increased (4 mm Hg) by closure of common iliac artery beyond the branch. b Can be increased in pressure (40 mm Hg) in renal artery following clamping of abdominal aorta just beyond the renal artery. c Very great increase in pressure (30 mm) in the left subclavian artery following ligation of thoracic aorta just beyond the subclavian artery.

tree and the larger the vessels involved the greater is the flow through the fistula the more rapid is the dilation of the heart, and the greater is the possibility of an early fatal effect. Potts' finds, for example that he cannot exceed a size of 4/16 inch in producing a fistula between the aorta and pulmonary artery without danger of cardiac failure. An arteriovenous fistula 1.5 cm in diameter introduced proximal to the trifurcation of the aorta in a dog is invariably fatal because of too great diversion of blood through the fistula and therefore through the heart whereas the same sized fistula in the femoral vessels is never immediately fatal.

CONCLUSIONS

The Lewis theory that a chemical substance originating in ischemic tissue or the Reid theory that "tissue needs" beyond the fistula excite the development of collateral circulation around an arteriovenous fistula are untenable since amputation of the potentially ischemic tissues beyond the fistula does not interfere with its development. The important condition for its development has been found to be ready access of blood to the site of the fistula by retrograde

site of ligation

The application of a band on the artery proximal to a fistula prevents dilatation of the artery by limiting the volume flow of blood through it. The application of a band on the vein proximal to a fistula results in the development of progressive edema of an elephantiasis nature.

These experiments indicate that the variable effects of an arteriovenous fistula observed clinically are due to variable conditions at the site of the fistula as imposed most probably by the deposition of fibrous tissue which by its contraction in the course of healing obstructs or limits the fistula itself or one or another of the four cardinal points of the fistula.

Again it has been proved that the circulatory phenomena accompanying an arteriovenous fistula can be attributed to the introduction into the arterial system of an area of lessened resistance through which blood flows more readily than through the capillary bed elsewhere and through which blood from a reservoir of high arterial pressure has direct access to a capacious venous bed of no or very low pressure which is in direct communication with the heart.

The collateral circulation which develops following ligation of a large artery depends upon transforming high end pressure in the parent artery into "lateral pressure" which, directed into its branches results in an increased volume flow through them. This increased volume flow distends them and opens up their prearteriolar and arteriolar beds whence the flow is directed into the prearteriolar beds of the branches distal to ligation whose low pressure because of the ligation permits blood to flow through them more readily than through prearteriolar beds elsewhere.

'End pressure' at a given point is directly proportional to the peripheral resistance beyond that point and must necessarily be greatest in the ascending

10 to 20 cc of the contrast medium in 3 to 5 seconds through a size 18 or 19 spinal needle. Air pressures of 50 to 60 pounds increased the rate of injection sufficiently to obtain satisfactory visualization of the collateral bed. Such studies were carried out immediately after fistulectomy and at subsequent intervals.

By using the contralateral leg as a control and visualizing both lower extremities on a single x-ray film any differences in filling technique between the initial and subsequent films were clearly demonstrated. Since slight shifts in the position of the legs caused some alteration in the pattern of the collateral beds a uniform position was adopted.

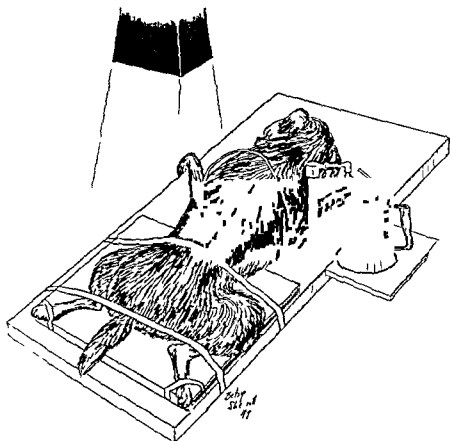


Fig 1—Illustration of the simple arrangement used in making an aortic injection. The injection apparatus is connected to the aortic needle by a light pressure tubing.

After some practice aortic puncture opposite the third or fourth left lumbar interspace was successfully accomplished by blind puncture in almost every instance.

The sudden increment in blood volume (that is 15 to 20 cc in 3 to 5 seconds) probably did not distend the collateral bed significantly. The injection apparatus devised by Doss⁹ was modified slightly to suit our purposes (Fig 1).

A STUDY OF THE COLLATERAL CIRCULATION AFTER EXCISION OF ARTERIOVENOUS FISTULAS

LEWIS H. BOSHER, JR., M.D., LUDWIG HARPER, M.D., AND
I. A. BIGGER, M.D., RICHMOND, VA.

AS A result of the abundant collateral circulation which develops in the region of an arteriovenous fistula, acute ischemic gangrene rarely follows excision of the fistulous area. However, in 1944 one of the authors (I. A. B.)¹ called attention to the frequency of chronic vascular insufficiency after fistulotomy and mentioned its occurrence despite the presence at operation of a strong Heubner Coenen sign, that is, pulsation of the distal arterial segment. Subsequently Herin, Harns, Rives and Davis,² Shumacker and Carter,³ and Freeman⁴ also reported a high incidence of chronic vascular insufficiency in cases in which excision necessitated interruption of the main artery to the extremity. Weakness of the extremity, easy fatigability, susceptibility to cold, intermittent claudication, color changes, muscular atrophy, and ulceration were mentioned as common sequelae. Some degree of vascular insufficiency occurred in certain cases even when sympathectomy had been done. The collateral circulation was adequate to the needs of the tissues at rest, but was insufficient to meet the demands of physical exercise. This was in contrast to the satisfactory results obtained by those procedures in which the lumen of the main artery was preserved.

To explain this vascular insufficiency Bigger suggested a regression of the arterial collateral bed following excision of arteriovenous fistulas. Holman⁵ had previously observed a reduction in the size of the proximal artery after fistulotomy in experimental and clinical cases. Reid⁶ had indicated that the postfistulotomy rise in surface temperature in the distal part was not sustained at the initial level. Freeman⁴ stated that oscillometric readings following repair of the artery were frequently greater immediately after the operation than some weeks later, but did not state whether the same applied to cases of excision.

The investigations reported here were undertaken to determine whether or not a regression of the collateral bed could be demonstrated in experimental animals.

TECHNIQUE

Fistulas usually 2 to 2.5 cm. in length were constructed by lateral anastomosis between the femoral vessels of young adult dogs just distal to the profunda branch. The fistulas were exercised after periods of from 6 weeks to 13 months. The functioning collateral vessels were demonstrated radiologically in the living animal under pentothal anesthesia by aortic injection of 70 per cent Neopax^{*} or 70 per cent Diodrast†. X-ray exposure was made after injection.

Recognition is due Dr. Chester Heald of Boston, Mass., and Dr. Richard Lester of Los Angeles for their technical assistance in Groups 3 and 4 of this work respectively.

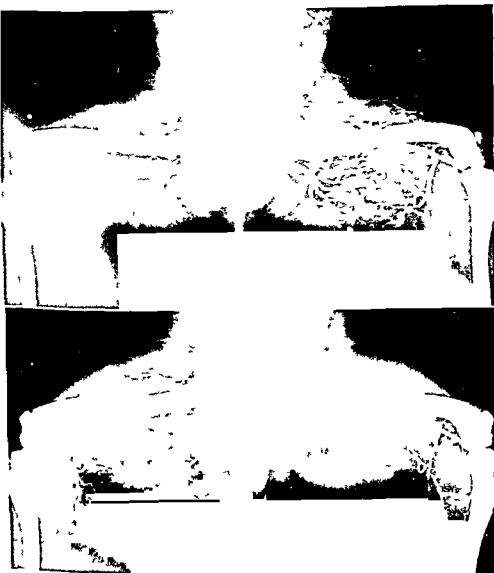
Read at the third annual meeting of the Society for Vascular Surgery, Atlantic City, N. J., June 1949.

A preliminary report of this investigation was presented in the Forum on Fundamental Surgical Problems before the Clinical Congress of the American College of Surgeons, New York, Sept. 11, 1948.

* Supplied by the Sclerolac Corporation, Elizabeth, N. J.
† Supplied by the Winthrop Chemical Company, Inc., New York, N. Y.

In dogs of this group, x-ray studies made as early as the fourth or fifth day after fistulectomy revealed a considerable regression in the main collateral bed and in the distal artery, but the proximal artery did not return to normal size until the second or third week.

1



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Fig. 1. — 1. Arteriogram made immediately after fistulectomy. Fistula on the right and location on the left present for 14 weeks. Note the much greater development of collaterals on the side of the fistula. The dilatation of the distal artery extends to the last major collateral branch in the thigh.

2. Arteriogram made 6 weeks after fistulectomy. A marked regression of the collateral bed on the side of the fistulectomy is now evident. There has been no change on the contralateral, ligated side.

We have encountered a few instances of thrombotic phlebitis following the aortic injection of 75 per cent Neopax. These animals were eliminated from the series. Where serial studies were contemplated, Neopax was preferred over Diodrast since the latter drug caused more retroperitoneal bleeding following withdrawal of the large needle from the aorta.

Vasospasm either as a result of the aortic injection or pentothal anesthesia could not be completely discounted, but the opposite leg served as a suitable control. Furthermore in almost all instances, as judged by the control leg, the filling technique was more satisfactory in follow up films. This was undoubtedly due to the regression of the large collateral bed on the side of the fistulectomy thus reducing the total vascular space to be filled.

EXPERIMENTAL RESULTS

Arteriograms made with the fistula patent are unsatisfactory since much of the contrast medium is shunted through the fistula, filling the venous as well as the arterial bed and producing a confusing maze of poorly defined dilated vessels. As stressed by Deterling, Essex and Waugh,¹⁰ a large proportion of the collateral vessels shown when the fistula is patent are venous channels. However, in addition to the large number of venous collaterals, an arterial bed can be demonstrated which is decidedly greater than that developed by ligation of the artery alone or with the concomitant vein.

Using the technique we have described, arteriograms made after excision of the fistula showed only the arterial collaterals. Immediately after fistulectomy a considerable enlargement of the main artery and its branches proximal to the site of the fistula could be demonstrated. In addition, the main artery distal to the fistula and those branches with anastomotic connections in the thigh showed constant dilatation. The intervening collaterals were more numerous, more dilated, and more tortuous than those which developed after simple ligation. The distal enlargement of the main artery terminated abruptly at the origin of the last major collateral branch in the thigh. No collateral vessels extended into the lower leg.

Group 1.—In Group 1 of this study the contralateral artery and vein were kept intact. The fistulas were maintained for 11 to 13 months before excision and the follow up period lasted 7 to 15 weeks.

In this group there were 6 dogs upon whom satisfactory studies were completed. Moderate to marked regression occurred in 5 while in 1 there was no regression. Further investigation indicated that the degree of regression varied directly with the extent of development of the collaterals.

In 1 animal in this group a thrombus had developed in the proximal artery so the fistula was being fed entirely by the distal artery. An extremely rich collateral bed resulted.

A rather profuse collateral bed developed but the dilatation of the individual vessels was somewhat less than in comparable fistulas of longer duration.

As a result of the contralateral ligation it was possible to compare the collaterals after resection with the collaterals developed by simple ligation.

Of the 8 dogs in this group the final collateral bed on the side of the fistulectomy was approximately equal to that on the contralateral ligated side in 4, slightly more extensive in 2 and slightly less in 2.

Group 3—Animals in Group 3 differed from those in the preceding group in that the contralateral ligation was performed at the time of constructing the fistula. The fistulas were of longer duration (15 to 20 weeks) but the follow up period lasted only 6 weeks.

The findings in the 4 dogs of this group were entirely consistent with those previously described. The final collateral bed on the side of the fistulectomy was equal to that on the contralateral side in 2 and slightly less on the side of the fistulectomy in 1. A satisfactory comparison was not possible in the fourth animal. Figs. 2 and 3 illustrate the results of the x ray studies in one of this group.

Group 4—In order to exclude any possible influence of the contrast medium on the regression of collaterals 3 animals were prepared as in Group 3, but no aortic injections were made immediately after fistulectomy. After intervals of time varying from 2½ to 10 weeks x ray studies were carried out and the animals then sacrificed. Pathologic examination of the collateral vessels was made.

In the animals of this group it was ascertained at the time of fistulectomy that a satisfactory collateral circulation had developed. Previous observations had shown that persistence of a strong thrill and distal pulsation after proximal occlusion of the artery correlated well with radiologic evidence of an extensive collateral bed.

The results in this group confirmed our impression that the contrast medium had not appreciably influenced the results.

The final collateral bed on the side of the fistulectomy was equal to that on the contralateral side in 2 dogs, slightly more extensive in 2 dogs and slightly less in 1.

Table I gives a comparative analysis of the opposite collateral beds in dogs of the last three groups.

TABLE I. COMPARISON OF FINAL COLLATERAL BEDS

CONDITION	NUMBER
Slightly better on side of fistulectomy	4
Approximately equal	5
Slightly better on contralateral ligated side	4

Findings of considerable interest have resulted from the limited pathologic investigation.¹¹ Briefly, the smaller collateral arteries chiefly 0.2 to 1.0 mm in diameter in the region of greatest collateral development show permanent organic changes. These changes consist primarily of minimal to marked fibrous tissue proliferation in the subendothelial zone and disruption and fragmentation

Group 2—In group 2 immediately after fistulectomy, and after the aortic injection the main vessels were ligated on the contralateral side. Fistulas were maintained for only 6 to 8 weeks before excision and the follow up period lasted only 8 weeks.

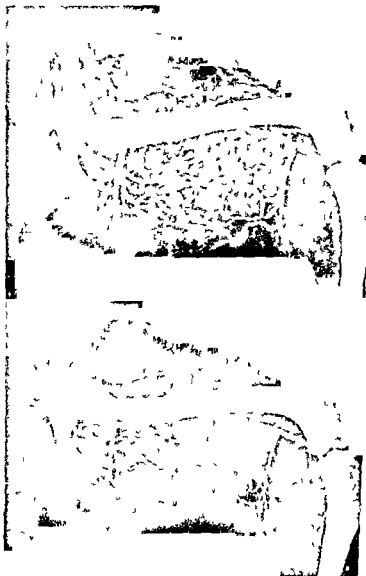


FIG. 3—4. An enlargement of the arteriogram illustrating the aneurysm of the aorta. The aneurysm is shown in the upper part of the image. The lower part of the image shows the aorta after fistulectomy, with the aneurysm removed and the vessel ligated on the contralateral side.

A rather profuse collateral bed developed but the dilatation of the individual vessels was somewhat less than in comparable fistulas of longer duration.

As a result of the contralateral ligation it was possible to compare the collaterals after regression with the collaterals developed by simple ligation.

Of the 8 dogs in this group the final collateral bed on the side of the fistulectomy was approximately equal to that on the contralateral ligated side in 4 slightly more extensive in 2 and slightly less in 2.

Group 3—Animals in Group 3 differed from those in the preceding group in that the contralateral ligation was performed at the time of constructing the fistula. The fistulas were of longer duration (15 to 20 weeks), but the follow up period lasted only 6 weeks.

The findings in the 4 dogs of this group were entirely consistent with those previously described. The final collateral bed on the side of the fistulectomy was equal to that on the contralateral side in 2 and slightly less on the side of the fistulectomy in 1. A satisfactory comparison was not possible in the fourth animal. Figs. 2 and 3 illustrate the results of the x-ray studies in one of this group.

Group 4—In order to exclude any possible influence of the contrast medium on the regression of collaterals 5 animals were prepared as in Group 3, but no aortic injections were made immediately after fistulectomy. After intervals of time varying from 2½ to 10 weeks x-ray studies were carried out and the animals then sacrificed. Pathologic examination of the collateral vessels was made.

In the animals of this group it was ascertained at the time of fistulectomy that a satisfactory collateral circulation had developed. Previous observations had shown that persistence of a strong thrill and distal pulsation after proximal occlusion of the artery correlated well with radiologic evidence of an extensive collateral bed.

The results in this group confirmed our impression that the contrast medium had not appreciably influenced the results.

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Findings of considerable interest have resulted from the limited pathologic investigation.¹¹ Briefly the smaller collateral arteries chiefly 0.2 to 1.0 mm in diameter in the region of greatest collateral development show permanent or aneurysmal changes. These changes consist primarily of minimal to marked fibrous tissue proliferation in the subendothelial zone and disruption and fragmentation

of the internal elastic membrane (Fig 4). The basic pathologic changes are present at the time of fistulectomy, but it is not yet known whether the proliferative process continues in the postfistulectomy period.



Fig 4—Illustration of a small artery (300 microns in diameter) in the region of the main collateral bed. Specimen taken in the postfistulectomy period. Note the subendothelial proliferation of fibrous tissue and the fragmentation of the internal elastic membrane. (Verhoeff van Gieson stain)

DISCUSSION

As previously stressed by many authors a variety of factors influence the extent of the collaterals developed in the presence of an arteriovenous fistula. These include the size and duration of the fistula, the amount of the surrounding scar tissue, and the individual response to the stimulus of the fistula. Of paramount importance also are the vascular pattern and the potential collateral anastomoses in the particular region in which the fistula is established. In this respect the collateral circulation to the lower extremity is more readily developed in the dog than in the human being. The lower extremity of the dog is relatively shorter than is that of the human being and the central artery of the aortic trifurcation in the former provides an excellent collateral supply through the pelvis. Gangrene of the distal leg cannot be produced in the dog by simple ligation of the main artery at any point. Mulvihill and Hurvey¹² showed that within 13 hours after ligation of the femoral artery of the dog the skin temperature of the foot had returned to normal. We are cognizant of these differences between the experimental animal and the human being in regard to the adequacy of the collateral circulation. Certainly more critical experiments than those reported here would be desirable.

We have been impressed with the constant enlargement of the distal artery even in animals with relatively small fistulas and with the proximal artery fully patent. This finding contrasts sharply with many case reports in the literature describing the distal artery as smaller than normal. In Groups 1 and 2 actual measurement and comparison with the intact contralateral artery in arteriograms confirmed the enlargement of the distal artery in every case except one. In this

instance the collateral bed was no greater than one would expect following simple ligation of the artery. Experimentally, Holman¹³ was able to cause a definite dilatation of the distal artery by constricting or occluding the proximal artery. He also noted the enlargement of the distal artery in the presence of large fistulas.

The constant enlargement of the distal artery undoubtedly signifies a retrograde flow. At the point of origin of the last major collateral branch in the thigh, where dilatation of the main artery ceases abruptly, a two directional flow must exist—proximally to the fistula and distally into the lower leg.

This retrograde flow plays an important part in the development of the collateral bed being responsible for the dilatation of those anastomotic vessels which arise distal to the fistula. Large channels are developed which divert blood away from the distal area into the fistula. In the absence of retrograde flow we would not expect a collateral bed greater than that developed after simple ligation of the artery.

However, after excision of the fistula these channels direct an abundant supply of blood into the distal tissues. Clinically, the appearance of palpable and visible pulse in the distal arteries is often noted after occlusion or excision of a fistula. Robertson, Dennis, and Elkin¹⁴ using plethysmographic methods in experimental animals, noted increases in distal blood flow up to 210 per cent greater than that existing before occlusion of the fistula.

The results of our present investigations indicate that this abundant blood flow does not persist long after the excision of the fistula. A marked contraction of the collateral bed has been demonstrated as early as 4 days after the fistulectomy and undoubtedly begins even sooner. At this time the distal artery and the collateral bed distal to the region of the fistula is already greatly reduced whereas the proximal artery does not return to normal for 2 or 3 weeks. The proximal artery is reduced in diameter below that of the normal intact collateral artery while the proximal collateral arteries remain slightly larger than normal thus indicating an increased blood flow around the obstructed area. The contraction of the collateral bed would seem to represent a recovery of normal vascular tone after elimination of the increased local blood flow—a primary myogenic response. Reduction in blood volume probably plays no significant role.

A marked regression of the collaterals occurred after fistulectomy in every animal that had developed an extensive collateral bed. In the majority of the animals the collateral bed regressed to a level approximately equivalent to or only slightly greater than that developed by simple ligation of the artery. Exact comparison of the final collaterals was not always easy since slight differences in position of the two legs caused some variation in the appearance of the vascular pattern. Nor could it be assumed that even under exactly similar circumstances identical collateral beds would be found in opposite legs of a normal animal. Not infrequently there was some persistence of the increased collateral anastomosis in the region of the extensor muscles of the knee on the side of the fistulectomy. This however is a region in which the collaterals were usually not strongly developed. Even when the final collateral bed on the side of the fistulectomy predominated the more numerous delicate and tortuous vessels often

is prevented from leaving the extremity and therefore an enlargement of the part results. This change in the volume of the leg is a measurement of blood flow and is recorded by connecting the boot with a recording capsule. In a series of some 15 animal repeated measurements were made prior to production of the fistula and at varying intervals following. Measurements taken with the fistula open revealed that the blood flow to the distal portion of the extremity was in many instances below normal. With occlusion of the fistula the blood flow to the distal part of the extremity was increased from 40 to 110 per cent. This increase in blood flow had no definite relationship to elapsed time although the greater increases were found in those animals with older lesions. In two instances the flow was less with the fistula occluded however in the first animal the fistula was of small size and had been greatly narrowed by fibrosis.

These studies presented are concerned only with the critical period following obliteration of the fistula and are not to be confused with the reversible changes about which Dr. Bocher speaks. It is my belief that after excision of an arteriovenous fistula involving a major artery there is some regression in blood flow below normal level and that the circulation in the extremity is below normal if a major vessel such as the popliteal or common femoral has been interrupted. I do think however that later there is a definite increase in flow which remains over what it was with the fistula present and is probably evidence that as we have all seen in our clinical experience with the healing of ulcers the healing of wounds and the general improvement in the appearance of the extremity. I believe that the ideal treatment of arteriovenous fistula would be repair of the artery but this procedure is frequently impossible. Following excision of an arteriovenous fistula and without sympathectomy we have not had an instance of gangrene.

A STUDY OF THE CARDIAC FRONTAL AREA IN PATIENTS WITH ARTERIOVENOUS FISTULAS

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THAT profound physiologic alterations of the cardiovascular system may occur in the presence of an arteriovenous fistula is well known, these changes have been the subject of intensive experimental and, to a lesser extent of clinical study. In extreme cases progressive cardiac dilatation and hypertrophy may take place with eventual failure of the heart. Although numerous instances of cardiac enlargement in cases of arteriovenous fistulas have been recorded in the literature, they are in large part reports of individual cases or small groups and no really large series has been studied. Consequently, such conclusions as have been reached concerning this phenomenon in patients have been based more on clinical impressions than on statistical data. For this reason, it was felt desirable to present a detailed analysis of studies of heart size before and after operative obliteration of the fistula in a large group of patients.

CLINICAL MATERIAL AND METHODS OF STUDY

The patients studied were a group of 145 soldiers with traumatic arteriovenous fistulas, incurred in all but a few instances as the result of battle injuries, all patients with fistulas in whom precise radiologic measurements of heart size were not available were excluded. Only one patient was a woman and most of the group as will be pointed out shortly were young adults.

The series does not include any case in which organic heart disease was known to exist. Many of the patients who had roentgenologic evidence of considerable increase in cardiac frontal area complained of no symptoms referable to the heart. A number of them however had dyspnea on exertion palpitation or distressing sensation of pounding of the heart especially when lying down. Only two instances of frank cardiac failure occurred and in one of these the episode took place before our first examination was made. This patient had two traumatic fistulas one involving the external iliac vessels the other the hypogastric vessels. The severe dyspnea orthopnea and edema had disappeared after resection of the first fistula in a hospital overseas. Though he still had evidence of cardiac enlargement he was relatively asymptomatic between the first and second operations. Excision of the hypogastric fistula brought about further decrease in heart size. The second patient who had been developing progressive increase in the cardiac frontal area became extremely orthopneic at the time of a *Streptococcus viridans* septicemia due to infection

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of the fistula, and a small pulmonary infarction. He was relieved of all symptoms and underwent a return of heart size to normal after excision of the fistula.²

Teleoroentgenograms were made in all patients generally both before and after operation. The predicted and actual frontal areas of the cardiac silhouette were calculated according to the method of Ungleider and Gubner,³ the calculations of the predicted values being made according to the height and weight of the patients on admission to the hospital.

Before operation, whenever the location of the fistula permitted it several determinations were made of the blood pressure and pulse rate changes during temporary digital occlusion of the fistula. The precise findings at operation were recorded in each case; in most instances these observations included measurement or careful estimation of the size of the fistula.

ANALYSIS OF DATA

Age Distribution—The patients were young adults ranging in age from 19 to 46 years with an average age of 24.5 years. There was no essential difference in the age of patients segregated into groups according to the location of the fistula (Table I).

Regional Distribution of the Fistulas—One hundred thirty-one patients had fistulas between vessels in the lower extremities or pelvis (Table I). For purpose of analysis these were divided into four groups. There were 53 with fistulas of the common femoral or femoral vessels. In 36 the popliteal vessels were involved. In 9 there was a fistula of such vessels as the hypogastric, obturator superior, gluteal or profunda femoral. In 33 the fistula involved vessels of the leg; in 23 of these the posterior tibial vessels were affected. In 54 cases the fistula involved vessels of the head, neck or upper extremity. For purpose of analysis these also were divided into 4 groups. There were 17 cases of fistulas of the subclavian or axillary vessels, 9 cases involving the brachial vessels, 14 cases involving the vertebral vessels or the common internal or external carotid artery and the corresponding vein, and 14 instances of fistulas of other vessels of the head, neck, and upper extremity.

TABLE I LOCATION OF LESION AND AGE DISTRIBUTION

LOCATION OF FISTULA	NUMBER OF CASES	AGE (YR.)	
		RANGE	AVERAGE
Pelvis and lower extremity	131	19-46	24
Femoral	53	19-34	22.4
Popliteal	36	19-45	25.8
Profunda femoris hypogastric obturator superior gluteal	9	20-27	22.9
Vessels of leg	33	19-34	25
Head, neck and upper extremity	54	20-46	25.6
Subclavian and axillary	17	20-41	29.7
Brachial	9	21-35	26
Carotid and vertebral	14	20-46	27
Other vessels of head, neck and upper extremity	14	20-34	27.7
Total	131	19-46	24.5

This group includes fistulas of the ulnar, radial, posterior circumflex humeral, thoracoacromial, subacromial, transverse cervical, occipital and lingual vessels.

TABLE II INTERVAL IN MONTHS BETWEEN INJURY AND PREOPERATIVE ROENTGENOGRAM
BETWEEN INJURY AND OPERATION AND BETWEEN OPERATION AND
1 POSTOPERATIVE ROENTGENOGRAM

	INTERVAL BETWEEN INJURY AND LAST PREOPERATIVE	INTERVAL BETWEEN INJURY AND	INTERVAL BETWEEN OPERATION AND FINAL POST OPERATIVE
LOCAL			
Pelvis and			
Femoral			
Proximal			
Proximal			
Vessels of			
Head and neck			
Subclavian			
Brachial			
Carotid and			
Other vessels			
Upper extremities			
All	0.7	4.6	0.130

Duration of the Fistula—The duration of the fistula at the time of the last preoperative roentgenogram varied widely from 0.7 to 26 months but there was remarkably little variation in the mean age of the fistula in the various groups (Table II). The fistulas of the lower extremity and pelvis averaged 4.6 months in age; those of the upper extremity, head and neck 4.5 months and the entire group 4.7 months. All of the larger groups had mean values of from 3 to 5 months. In 2 small groups the mean age of the fistula was a little greater. The interval of time elapsing between injury and operative cure of the fistula also varied widely from 1 week to 30 months but again there was little difference in the average age of the fistula in the various groups. In all the larger groups this value ranged from 4.4 to 5.7 months. The average age of the fistula at the time of surgery was 5.5 months in the case of lesions of the lower extremities or pelvis and 5.3 months in the case of lesions of the head and neck or upper extremity. Similarly the time elapsing between the operation and the

TABLE III PROPORTIONATE DISTRIBUTION OF PREOPERATIVE MEASUREMENTS OF CAROTID
FRONTAL AREA

	NUMBER OF	ACTUAL FRONTAL AREA						
Proximal femoral hypo-	6	0	0	0	0	16.7	87.3	0
gastric etc.	30	2	66	23	96.9	56.1	59.8	3
Vessels of leg								
Head and neck and upper extrem-	45		11.1	18.1	4.1	38	55.1	1
ity								
Subclavian and axillary	1	0	0	0	15.4	1	77.0	0
Brachial	11	11.1	0	44.4	44.4	55.5	53.4	11.1
Carotid and vertebral	11	0	0	0	3	45.5	45.4	9.1
Other vessels of head and neck	1	0	0	15	33.3	31.3	58.4	8.3
and upper extremity								
Total	151	11.8	3.3	1.4	41.8	54.9	41.8	

All actual measurements of carotid frontal area are expressed in percentage of preoperative value

TABLE IV PROPORTIONATE DISTRIBUTION OF POSTOPERATIVE MEASUREMENTS OF CARDIAC FRONTAL AREA

LOCATION OF FISTULA	NUMBER OF CASES	ACTUAL FRONTAL AREA					
		1-1+	110+	111+	106+	80-100	<80
Pelvis and lower extremity	115	59	11	18	28	60	65
Femoral	31	78	13	21	31	64	39
Iliofemoral	31	97	9	5	3	68	97
Iliofemoral femoral hypogastric etc	8	0	0	0	11	60	20
Vessel of leg	28	0	7	10	21	70	20
Head neck and upper extremity	4	0	0	4	3	60	13
Subclavian and axillary	10	0	0	6	7	46	27
Brachial	4	0	0	0	2	75	0
Carotid and vertebral	11	0	0	0	9	27	18
Other vessels of head neck and upper extremity	13	0	0	7	20	92	0
Total	161	43	31	14	26	64	8

All actual measurements of cardiac frontal area are expressed in percentages of predicted area

final roentgenogram varied from a few days to 8 months but the mean value in all groups fell between 3 weeks and 22 months that for lesions of the head, neck, and upper extremity being 15 months and that for lesions of the lower extremity and pelvis being 16 months

MEASUREMENTS OF THE CARDIAC FRONTAL AREA

Records of preoperative measurements of cardiac frontal area were available for study in 153 of the 185 cases of arteriovenous fistula postoperative measurements in 161 and both pre and postoperative measurements in 132 (Tables III, IV and V)

Control Measurements—No true control studies were carried out since the cardiac frontal area was not measured in a large series of soldiers without arteriovenous fistulas but otherwise similar in physical and nutritional state to those who form the basis of this study For what value it might be however

TABLE V PROPORTIONATE DISTRIBUTION OF POSTOPERATIVE CHANGES IN CARDIAC FRONTAL AREA

LOCATION OF FISTULA	NUMBER OF CASES	DECREASE				ESSENTIAL CHANGE*	INCREASE
		1+	11+	11+	1+	20	0+
Pelvis and lower extremity	115	10	13	44	6	30	4
Femoral	31	13	41	50	5	18	20
Iliofemoral	29	17	31	50	65	20	60
Iliofemoral femoral hypogastric etc	8	0	14	40	40	50	0
Vessels of leg	28	0	4	40	44	50	4
Head neck and upper extremity	4	0	10	30	40	50	3
Subclavian and axillary	10	0	50	40	40	60	0
Brachial	4	0	0	25	20	50	20
Carotid and vertebral	9	11	0	22	44	50	0
Other vessels of head neck and upper extremity	10	0	10	40	50	50	0
Total	161	28	50	40	50	50	38

All changes are expressed in percentage change from preoperative values

data derived from analysis of the final postoperative measurements of cardiac frontal area in 119 patients cured of arteriovenous fistulas in whom the preoperative measurements had not exceeded 115 per cent of the predicted value are presented in Fig 1. The cases omitted are those in which there was great increase in heart size before operation, the cases in which it seemed most likely that hypertrophy as well as dilatation of the heart might have occurred and in which some degree of enlargement might have persisted after operation. It is evident that in this group of patients the values tended to center around the figure 95 per cent of the calculated predicted value. There were 74.8 per cent with actual values ranging from 85 to 105 per cent of the predicted, while in

• CARDIAC FRONTAL AREA IN PER CENT OF PREDICTED

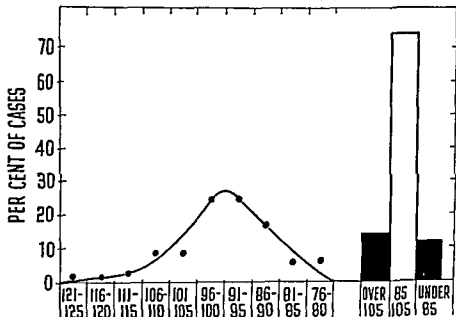


Fig 1.—Distribution of measurements of cardiac frontal area (in terms of predicted area) after operative cure of arteriovenous fistula in 119 patients in whom the preoperative measurement had not exceeded 115 per cent of the predicted. Note that the majority of the values fall within the 85 to 105 per cent range.

11.8 per cent values of less than 80 per cent and 13.4 per cent values greater than 105 per cent obtained. If, on the other hand, 100 per cent were used as the 'normal' value a smaller number had values within plus or minus 10 per cent (69.7 per cent) and the remainder were less evenly distributed, only 5 per cent having values in excess of 110 per cent while 25.2 per cent had values of less than 90 per cent of the predicted.

COMPARISON OF PRE AND POSTOPERATIVE MEASUREMENTS OF THE CARDIAC FRONTAL AREA

In Tables III and IV and Figs 2 and 3 are summarized the data regarding the final measurements of cardiac frontal area before and after operative

•CARDIAC FRONTAL AREA IN PER CENT OF PREDICTED

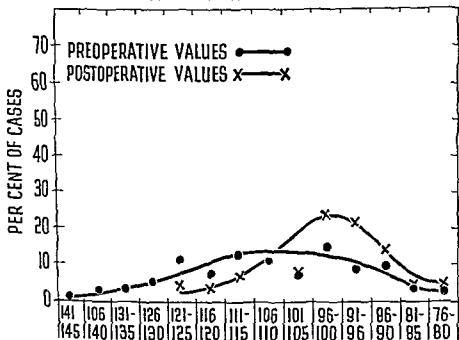


Fig. 1.—Distribution of measurements of cardiac frontal area (in terms of predicted area) in 153 cases before and in 161 cases after operative cure of arteriovenous fistula.

•PER CENT OF PREDICTED HEART SIZE

PREOPERATIVE VALUES (hatched bars) POSTOPERATIVE VALUES (solid bars)

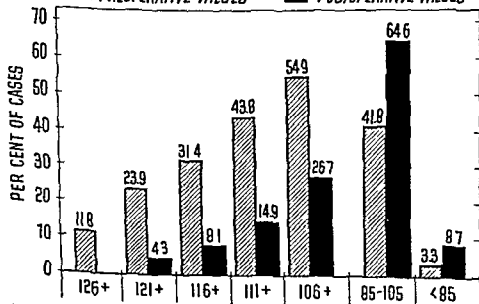


Fig. 2.—Proportionate distribution of measurements of cardiac frontal area in percentage of predicted area in 153 patients before and in 161 patients after operative cure of arteriovenous fistula.

obliteration of the arteriovenous fistula. Before operation 14.9 per cent of the patients had actual values in excess of 105 per cent of the predicted, 43.8 per cent in excess of 110 per cent, 31.4 in excess of 115 per cent, 23.9 in excess of 120 per cent, and 11.8 per cent in excess of 125 per cent of the predicted. In contrast postoperative values were in excess of 105 per cent of the predicted in only 26.7 per cent of the patients, in excess of 110 in only 14.9 per cent, in excess of 115 in only 8.1 per cent, and in excess of 120 per cent of the predicted in only 4.3 per cent. Before operation the values ranged from 85 to 105 per cent of the predicted in 41.8 per cent and were less than 85 per cent of the predicted in 33 per cent. After operation these values were 64.6 and 8.7 per cent respectively.

• POST OPERATIVE CHANGE IN HEART SIZE EXPRESSED IN PER CENT INCREASE AND DECREASE OF PREOPERATIVE VALUES

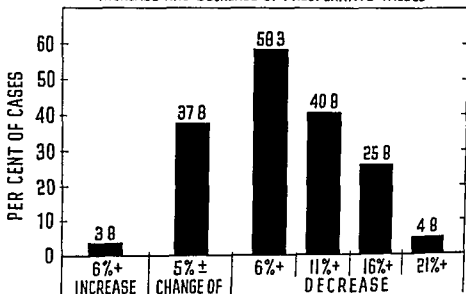


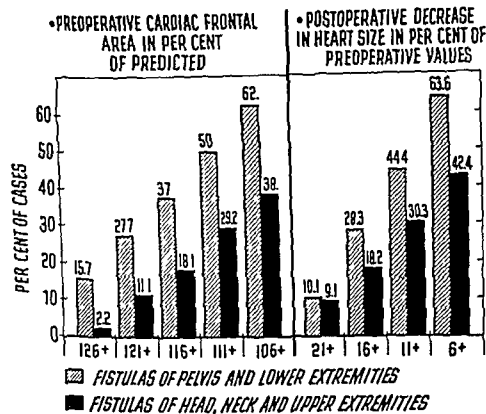
Fig. 4.—Proportional distribution of postoperative alteration in cardiac frontal area in 15 cases of arteriovenous fistula.

In Table V and Fig. 4 the data are summarized with regard to the percent age change in heart size after operation compared to the preoperative measurements. There was no essential change in 37.8 per cent of cases while in 3.8 per cent a slight increase in heart size was recorded. Nearly 60 per cent showed a reduction of 6 per cent or more, about 41 per cent a reduction of 11 per cent or more, about 26 per cent a decrease of 16 per cent or more, and about 10 per cent a decrease of 21 per cent or more.

FACTORS POSSIBLY INFLUENCING PRE- AND POSTOPERATIVE CARDIAC MEASUREMENTS

On comparing the pre- and postoperative values of cardiac frontal area in the various groups (Tables III and IV and Fig. 5) wide differences were in

mediately apparent. In general, the patients with femoral and popliteal fistulas tended to have larger hearts before operation than those with fistulas in other locations. As a rule, cardiac enlargement was more common in patients with fistulas of the pelvis and lower extremities than in those with fistulas of the head, neck, and upper extremity. When these two groups are compared with regard to the degree of reduction in heart size after operation, the same difference is noted but to a slightly lesser degree (Table V and Fig. 5).



In addition, there seemed to be a direct general relationship between the size of the fistula and the degree of cardiac enlargement. For example, the group with fistulas in the leg, which were generally small, is compared with the femoral or popliteal fistulas, showed less cardiac enlargement than the group with femoral or popliteal lesions. In order to evaluate the factor of size of fistula more properly, the data on 67 patients with femoral and popliteal fistulas of known size were analyzed (Table VI). Other factors such as duration of the lesion were similar in the two groups. It is evident that those with larger

TABLE VI PROPORTIONATE DISTRIBUTION OF CARDIAC ENLARGEMENT IN RELATION TO SIZE OF FISTULA IN CASES OF FEMORAL AND POPLITEAL FISTULAS

LOCATION OF FISTULA	NUMBER OF CASES	SIZE OF FISTULA (IN MM)	CARDIAC FRONTAL AREA				
			120+	121+	116+	111+	106+
Popliteal	17	>8	17 6	33 3	41 1	61 1	70 8
Popliteal	14	<8	14 3	14 3	14 4	31 7	64 4
Femoral	23	>8	30 4	50 2	10 1	87	91 7
Femoral	13	<8	1 1	46 2	46 2	61 5	6 9
Both	40	>8	20 0	45	55	17 5	85
Both	27	<8	18 5	25 6	33 1	48 1	10 4

All measurements of cardiac frontal area are expressed in percentage of predicted area

fistulas tended to show more cardiac enlargement. If popliteal and femoral fistulas of roughly the same size are compared, it seems evident that the femoral fistulas were associated with more cardiac enlargement, the femoral arteries were the larger in diameter and the femoral fistulas were closer to the heart. Indeed, the increase in heart size was as great in the smaller femoral fistulas as in the larger popliteal fistulas. In Table VII are summarized data concerning preoperative heart size in subclavian and axillary, popliteal, and femoral fistulas of large size and of moderate duration. They suggest that the femoral fistulas tended to cause the greatest increase in cardiac size and the subclavian and axillary fistulas the least. The femoral vessels were larger than the others, the popliteal and the axillary and subclavian vessels were roughly equal in size. The subclavian and axillary fistulas were closest to the heart, the popliteal fistulas the most distant.

TABLE VII PROPORTIONATE DISTRIBUTION OF PREOPERATIVE CARDIAC FRONTAL AREA IN VARIOUSLY LOCATED FISTULAS 7 MILLIMETERS OR MORE IN DIAMETER AND OF FROM 31 TO 65 MONTHS DURATION

CARDIAC FRONTAL AREA				
<105		106-115		116+
NUMBER	PERCENT	NUMBER	PERCENT	NUMBER
164	16.4	156	15.6	

In Table VIII the relationship of the duration and size of the fistula to the preoperative cardiac frontal area is analyzed. With regard to the cases of popliteal fistula, in which the time element was essentially the same, the size of the heart could be correlated with the size of the fistula: smaller fistulas were associated with smaller heart size and larger fistulas with larger heart size. The cases of femoral fistula associated with the greatest increase in cardiac frontal area had larger fistulas of longer duration than those associated with less cardiac enlargement. When cases of popliteal and femoral fistulas of large size were studied with respect to the relationship of duration of the lesion and increase in cardiac frontal area (Table IX) there seemed to exist a definite correlation: the cases with greatest increase in cardiac frontal area having a larger proportion of cases of relatively long duration.

TABLE VIII RELATIONSHIP OF DURATION AND SIZE OF FISTULA TO PREOPERATIVE SIZE OF HEART

LOCATION OF FISTULA	CARDIAC FRONTAL AREA 110% OF PREDICTED OR LESS					CARDIAC FRONTAL AREA 111% OF PREDICTED OR MORE				
	NUMBER OF CASES	AVERAGE SIZE FISTULA (IN MM)	DURATION OF FISTULA		PER CENT OF CASES OF 5 MO DURATION OF MORE	NUMBER OF CASES	AVERAGE SIZE FISTULA (IN MM)	DURATION OF FISTULA		PER CENT OF CASES OF 5 MO DURATION OF MORE
			RANGE (IN MO)	AVERAGE (IN MO)				RANGE (IN MO)	AVERAGE (IN MO)	
Popliteal	15	4	1 to 10	5	40	16	9.0	2 to 10	4.6	31.2
Femoral	8	6.7	2 to 8	4.0	12.5	8	9.2	1 to 19	8.3	39.3

TABLE IX RELATIONSHIP OF DURATION OF FISTULA TO PREOPERATIVE CARDIAC FRONTAL AREA IN CASES OF POPLITEAL AND FEMORAL FISTULA OF LARGE SIZE (DIAMETER OF 7 MM+)

LOCATION OF FISTULA	NUMBER OF CASES	PER CENT OF CASES										
		PEP	BER OF	PER	BER OF	PET	BER OF	PEP	BER OF	PER	BER OF	PEP
Popliteal	14	—	—	—	—	—	—	—	—	—	—	—
Femoral	14	—	—	—	—	—	—	—	—	—	—	—
Both	28	—	—	—	—	—	—	—	—	—	—	—

When more than one measurement of cardiac frontal area was made before operation 11 or 28.2 per cent showed an increase in heart size of more than 5 per cent on the second examination, while in 4 or 10.3 per cent there occurred a decrease and in 24, or 61.5 per cent, no essential change occurred (Table X). It may be significant that an increase in heart size was noted on the second examination in 8 of the 14 instances in which the interval between the two examinations was 6 weeks or more. When more than one measurement of cardiac frontal area was made after operation (Table XI) 6 or 25 per cent showed a decrease of more than 5 per cent on the last examination, 1, or 4.2 per cent, an increase while in 17 or 70.8 per cent no essential change was noted. In nearly two thirds the interval between the two examinations was 1 month or more.

In Fig. 6 the heart size is correlated with pulse and blood pressure response to temporary occlusion of the fistula. Only from 20 to 30 per cent of those with minimal or moderate response showed marked cardiac enlargement while from 26 to 32 per cent showed lesser degrees of cardiac enlargement. On the other hand in those cases with marked pulse and pressure changes during occlusion from 47 to 61 per cent showed rather marked cardiac enlargement and an additional 19 to 23 per cent showed a slight or moderate increase in heart size.

•RESPONSE TO OCCLUSION OF FISTULA

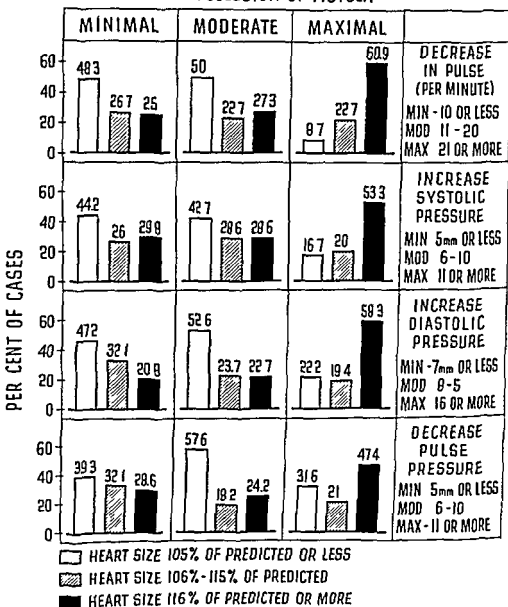


Fig. 6—Comparative measurements of earlase frontal area (in percentage of predicted value) in 145 cases of arteriovenous fistula in relation to magnitude of response of pulse and blood pressure to temporary occlusion of the fistula.

TABLE X. COMPARISON OF CARDIAC FRONTAL AREA IN CASES IN WHICH MORE THAN ONE MEASUREMENT WAS MADE BEFORE OPERATION

LOCATION OF FISTULA	SIZE OF FISTULA (IN MM.)	FIRST EXAMINATION		LAST EXAMINATION	
		DURATION OF FISTULA (IN MO.)	SIZE OF HEART (IN PEP. CENT. OF PREDICTED)	DURATION OF FISTULA (IN MO.)	SIZE OF HEART (IN PEP. CENT. OF PREDICTED)
Femoral	10	17	109	32	126
Femoral	5	28	120	32	127
Femoral	9	30	81	40	114
Femoral	9	10	110	20	110
Femoral	-	24	124	36	124
Femoral	15	02	102	120	122
Femoral	8	51	118	65	118
Femoral	8	27	118	47	110
Femoral	10	20	114	45	114
Femoral	6	20	126	40	126
Femoral	6	35	100	70	127
Femoral	10	20	111	60	111
Femoral	10	30	104	40	124
Femoral	12	20	121	43	121
Popliteal	8	10	105	3	116
Popliteal	5	30	92	6	108
Popliteal	10	27	127	37	127
Popliteal	5	40	108	58	108
Popliteal	-	14	93	25	93
Popliteal	-	4	114	58	110
Popliteal	-	4	119	48	121
Popliteal	10	35	125	45	125
Popliteal	5	42	110	64	130
Popliteal	10	64	127	8	132
Popliteal	10	27	105	46	112
Popliteal	10	27	113	40	102
Popliteal	15	24	125	44	125
Profunda	4	20	92	60	92
Femoral	-	-	-	-	-
Scap. gluteal	5	53	100	62	92
Obturator	2	20	116	50	107
Emulgate	2	5	107	60	107
Post. tibial	2	22	101	40	97
Post. tibial	2	18	97	27	97
Post. tibial	2	25	84	25	90
Post. tibial	-	32	90	45	90
Subclavian	10	21	67	45	100
Axillary	-	2	88	38	90
Int. carotid	-	1	94	3	115
Ulnar	-	7	107	15	118

DISCUSSION

Although it is well recognized that arteriovenous fistulas are likely to cause an increase in cardiac output, enlargement of the heart, and in certain instances failure, this potentiality in patients with fistulas has been generally appreciated only during the last quarter of a century. Concerning this matter Reid¹ wrote in 1925: "It has taken the profession a long time to establish a cause and effect between arteriovenous fistulas in vessels smaller than the aorta and the cardiac disturbances they produce. So often we remain blind to the insidious conditions that shorten the duration of human lives. Although Osler for years followed two cases of arteriovenous aneurysms (one axillary, the other femoral) in which the patients died from cardiac disease at the early ages of 29 and 46

• RESPONSE TO OCCLUSION OF FISTULA

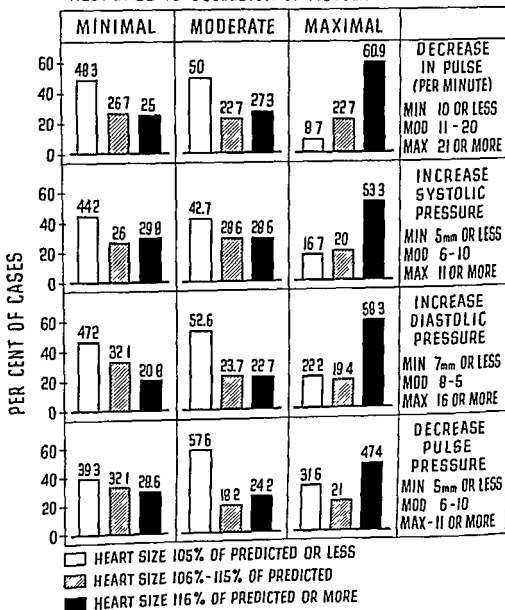


Fig. 6.—Comparative measurements of carotid frontal area (in percentage of predicted value) in 14 cases of arteriovenous fistula in relation to magnitude of response of pulse and blood pressure to temporary occlusion of the fistula.

the twenties based upon limited clinical observations but supported by the important experimental contributions of such men as Reid⁷ and Holman.⁸ A number of instances of cardiac enlargement and of failure of the heart have been reported especially in the past twenty five years. Though most of the instances of frank heart failure have been in long standing cases of large arteriovenous fistulas, a number of cases have been recorded in which failure occurred very soon, for example, the remarkable case of Mason⁹ in which failure was present within a few weeks of the onset of a traumatic subclavian fistula.

With regard to the incidence of cardiac enlargement in patients with arteriovenous fistulas there is little information in the literature. Holman noted that although cardiac dilatation and hypertrophy had been recorded as present in only 4 per cent of the 447 cases collected by Callander such changes were found in 28 per cent of the 21 cases he reviewed from the Johns Hopkins Hospital. Pendergrass¹⁰ examined 32 patients whose fistulas were obliterated by surgical means and found that 27 (84.3 per cent) showed an average decrease in cardiac diameter of 1.18 cm. while one patient showed an increase and 4 (12.5 per cent) no change. In the present study the cardiac frontal area in a fairly large series of patients with arteriovenous fistulas has been analyzed.

The method proposed by Ungelerder and Gubner was utilized for measuring the heart size. This method has proved as reliable as any for estimating heart size. In calculating the predicted frontal area the height and weight of the patient upon admission were employed and the values so calculated were used in each patient for determining the per cent of the predicted value in all subsequent examinations. Had the predicted value been recalculated at each examination from the height and weight of the patient at that time succeeding examinations would have revealed an apparent decrease in the per cent of the predicted area in the majority of instances if no change had actually occurred, since most of the patients gained weight after admission and according to the tables for estimation the predicted frontal area for a patient of any given height increases as the weight increases.

It is unfortunate that no normal values in a similar group of young soldiers without fistula in a comparable state of nutrition were available for study. The tables used for determination of the normal predicted area are based upon 100 per cent as normal and it has been generally accepted that values are abnormal if they differ from the predicted by 10 per cent. In looking over the values obtained in our patients after operation, it appeared that they included a great many which would thus be considered less than normal in size. We therefore analyzed these values excluding those with marked preoperative enlargement—cases in which cardiac hypertrophy might conceivably have occurred and in which a return to normal might not take place after operation. We found indeed that they did tend to center around the figure 95 per cent of the predicted area rather than around the value 100 per cent of the predicted. Those which were without the limits plus or minus 10 per cent of this control value were evenly distributed about one half of them exceeding and one half being less than these values. Though such a study does not con-

TABLE VI COMPARISON OF CARDIAC FRONTAL AREA IN CASES IN WHICH MORE THAN ONE MEASUREMENT WAS MADE AFTER OPERATION

LOCATION OF FISTULA	FIRST EXAMINATION		SECOND EXAMINATION	
	INTERVAL AFTER OPERATION (IN MO)	CHANGE IN HEART SIZE FROM PREOPERATIVE VALUE	INTERVAL AFTER OPERATION (IN MO)	CHANGE IN HEART SIZE FROM PREOPERATIVE VALUE
Femoral	0.16	1 1/4% decrease	6.0	19% decrease
Femoral	0.3	21% decrease	-	21% decrease
Femoral	2	4% increase	3.7	4% increase
Femoral	0.5	14% decrease	3.5	16% decrease
Femoral	0.7	12% decrease	4.7	17% decrease
Femoral	1.0	-	4.7	16% decrease
Femoral	0.4	8% decrease	2.7	16% decrease
Femoral	0.7	30% decrease	2.8	30% decrease
Popliteal	1.3	21% decrease	2.5	16% decrease
Popliteal	1.7	12% decrease	4.0	12% decrease
Popliteal	1.0	15% decrease	2.6	14% decrease
Iliopopliteal	0.4	4% decrease	7.0	4% decrease
Popliteal	0.4	13% decrease	8.0	13% decrease
Post tibial	0.7	18% decrease	1.6	16% decrease
Post tibial	0.7	-	0.8	9% decrease
Cenulato	0.5	2% decrease	1.2	6% decrease
Subclavian	1.5	-	3.0	1% decrease
Subclavian	1.0	4% decrease	1.5	-
Axillary	0.4	-	1.0	-
Axillary	0.7	4% decrease	4.0	20% decrease
Brachial	0.5	16% increase	1.5	8% increase
Ulnar	0.2	24% increase	2	24% increase
Ulnar	1.0	13% decrease	1.6	13% decrease
Subscapular	0.1	8% decrease	1.0	20% decrease

he was never unless possibly shortly before his death convinced of the causal relationship existing between the two conditions and for a long time he counseled against operations on arteriovenous aneurysms. In his *Remarks on Arteriovenous Aneurysm*,¹⁴ Osler had stated, "We all agree I think with the conclusion arrived at by Subbotich senior surgeon of the Belgrade State Hospital, from his experience in the Balkan War. That arteriovenous aneurysms should be operated upon, as they offer small prospect of spontaneous cure although they often remain stationary for a long time and cause relatively little trouble." Yet he must have been lukewarm regarding this point to say the least since in reference to one patient he said "The tumor had increased and the question was whether it was safe to leave him alone. This was the policy I urged strongly. Twice he narrowly escaped operation." In enumerating the end results in fistulas he did not mention at all the possibility of cardiac strain and failure. Later in the same paper he did state that remote effects on the general circulation are rare particularly in aneurysms of the vessels of the head and arms. One of my patients (Case 3) died from heart disease which may have had some connection with his long standing lesion. I feel confident that Reid referred to Osler's opinion in the same light as I as an expression of the best medical opinion of the time by its acknowledged leader.

Through the writings of Matas,⁶ Reid,⁸ Holman⁹ and others the profound effects of arteriovenous fistulas upon the heart were forcefully pointed out in

authors have stated that such changes were less likely to occur in patients with fistulas of the head, neck, and upper extremities in spite of the limited number of observations available to them. As we have previously mentioned Osler who was not impressed to say the least with the important relationship between arteriovenous fistulas and cardiac strain stated that remote effects upon the general circulation were rare particularly in aneurysms of the vessels of the head and arms. Our study did not provide us with an adequate explanation for these interesting observations. The theories which can be postulated to explain them lend themselves to experimental confirmation or refutation. Such experiments are being initiated and give promise of providing an adequate explanation for this curious phenomenon.

The studies presented demonstrate that when there is a marked change in pulse or blood pressure upon temporary occlusion of the fistula there is likely to be early significant increase in heart size. They show that without other information one can gain some idea of the likelihood of early cardiac enlargement from the location of the fistula alone. Though considerable increase in heart size may occur relatively soon after the development of an arteriovenous fistula of any reasonably large vessels in any portion of the body, such a change is particularly likely to take place in patients with fistulas involving the great vessels caudad to the heart.

SUMMARY AND CONCLUSIONS

A series of young soldiers with peripheral arteriovenous fistulas of relatively short duration has been analyzed with respect to enlargement of the heart. Cardiac enlargement was noted in a large number before operative excision of the fistula and reduction in heart size occurred in a comparable number after operation. It appeared that the location of the fistula with respect to whether it were caudad or cephalad to the heart, the size of the artery involved, the size and age of the fistula, and the magnitude of the pulse and blood pressure response to temporary occlusion of the fistula could be correlated with the tendency to early development of cardiac enlargement.

REFERENCES

- 1 Shumaker H B Jr, Welford N T and Carter K L. Streptococcus Viridans Septicemia From Vegetations in Femoral Arteriovenous Aneurysm. Report of Case Cured by Surgical Excision of the Aneurysm. Ann. Surg. 124: 12, 1946.
- 2 Langeleir H E and Tubner R. Evaluation of Heart Size Measurement. Am. Heart J. 24: 404, 1942.
- 3 Neil M L. The Effects of Abnormal Arteriovenous Communications on the Heart, Blood Vessels and Other Structure. Arch. Surg. 11: 254, 1920.
- 4 Osler W. Remarks on Arteriovenous Aneurysm. Lancet 1: 949, 1911.
- 5 Mata R. On the Systemic or Cardiovascular Effect of Arteriovenous Fistulae. A General Discussion Based Upon the Author's Surgical Experience. Trans. South. S. A. 36: 1, 1920.
- 6 Holman F. The Physiology of an Arteriovenous Fistula. Arch. Surg. 7: 648, 1922.
- 7 Neil M L. The Effect of Arteriovenous Fistula Upon the Heart and Blood Vessels.
- 8 Holman F.
- 9 Mata R.
- 10 Pence

III Cardiac Dilatation and
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stitute satisfactory normal control observations it does lend some additional meaning to the enlargement of the heart so commonly noted in the subjects with arteriovenous communications.

Our studies reveal conclusively that demonstrable evidence of enlargement of the heart was present in about one half of a group of young subjects with peripheral arteriovenous fistulas of relatively short duration few of whom had symptoms of cardiac strain and who, for all practical purposes had no evidence of cardiac failure. This fact was confirmed by evidence of measurable reduction in cardiac size after operation in a comparable percentage.

Further analysis of these data tend to confirm some opinions held concerning factors which influence the development of cardiac enlargement in the presence of an arteriovenous fistula opinions based largely upon experimental work but supplemented in part by clinical observations. In the first place it is evident that a definite relationship existed between the size of the fistula and the degree of cardiac enlargement particularly with reference to fistulas of vessels of the pelvis and lower extremities. In the second place, they demonstrate that there was a relationship between the age of the fistula and the cardiac enlargement. When other variable factors were controlled by proper sampling of cases of femoral and popliteal fistulas cardiac enlargement appeared to vary directly with the duration of the lesion. When two or more roentgenograms were made in any given case at intervals of six weeks or more before operation more than one half showed demonstrable increase in heart size on the last examination.

It has often been stated that the distance of the fistula from the heart is an important factor in the resultant increase in cardiac size greater changes tending to occur the nearer the fistula to the heart. The conclusions reached from some of the experimental work offered in support of this thesis can perhaps be challenged in part because of failure to take into consideration the size of the artery in communication with the vein arteries of successively larger caliber having generally been used the closer to the heart the fistula was made. It is apparent for example that if the diameter of the fistula exceeds that of the parent artery the blood flow through the fistula will be limited in part by the size of the parent artery. Our data on change in heart size in femoral and popliteal fistulas would tend to support the view that the nearer the fistula to the heart the greater is the tendency to early cardiac enlargement. It is felt however that here again too much importance cannot be attached to this relationship since the caliber of the vessels may perhaps also have been a factor. It would seem highly desirable to inquire further into this matter by controlled experimentation.

Our clinical observations demonstrated that at least one other factor was more important than the proximity of the fistula to the heart namely the location of the fistula with respect to whether it was cephalad or caudad to the heart. It was clear that the incidence and degree of cardiac enlargement or the rapidity with which enlargement took place was less in those patients with fistulas of the head neck and upper extremities than in those with fistulas of the pelvis and lower extremities. It is of considerable interest that several

THE EXPERIMENTAL AND CLINICAL USE OF VEIN GRAFTS TO REPLACE DEFECTS OF LARGE ARTERIES

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THE use of vein grafts to replace arterial defects was first explored by Carrel and his associates nearly fifty years ago.^{1, 2} Some dilatation and thickening of the grafts were observed within two weeks. Further thickening occurred during ensuing months and the grafts were said to take on the appearance of arteries. Microscopically the thickening was found to be due to an increase of fibrous tissue in the middle coat and in the inner layer of the outer coat of the grafts. These observations were confirmed by Watts³ and further extended by Carrel⁴ and Guthrie.⁵ Although some dilatation of the grafts uniformly occurred, it was thought to be limited by the increase of fibrous tissue in the vein wall.⁶ Before the beginning of World War I vein grafting had been successfully performed both experimentally and clinically.^{7, 8} It was rarely attempted in battle wounds, however, because of the difficulties under which war surgery was done and the fear of infection.⁹ During World War II Blakemore, Lord, and Stefko¹⁰ proposed their nonsuture method of vein grafting, a modification of the technique originally described by Pirie¹¹ and Hopfinger.¹² This method was available for use in only a few patients in the Armed Forces and the results unfortunately were less satisfactory than had been hoped for.¹³

Despite the indifferent success in emergency military surgery, the use of vein grafting may offer the solution to a difficult problem when the civilian surgeon is confronted with a defect of a critical artery. The recent use of vein grafts by Blakemore¹⁴ in reconstructive aneurysmorrhaphy and by Fontaine¹⁵ in arteriosclerosis obliterans has extended their field of usefulness in elective surgery.

Interest in the use of stored arterial isografts first extensively studied by Carrel¹⁶ from 1907-1910 has been revived by Gross, Hurwitt, Bill, and Peirce^{17a} whose early clinical results have been encouraging. Carrel had success with 75 to 80 per cent of his animal grafts while Gross and his co-workers^{17b} reported thrombosis of one and intimal sclerosis in another of seventeen dog aortic isografts using a somewhat different solution for storage. The use of smaller arteries by Carrel (carotids in dogs) may have accounted for most of his failures. If stored artery isografts prove to function satisfactorily without serious degenerative changes occurring as a result of tissue incompatibility, it may be that they will prove to be preferable to vein grafts.

DISCUSSION

DR HOLMAN—Any other discussion? I would like to ask Dr Shumacker how he is going to study the effect of gravity in his experimental work.

DR SHUMACKER—I agree with the discussors that it is certainly true that the directness of the venous return is very important. We have had experimental animals in which simple ligation of the proximal vein has reduced the cardiac output to one half the level that previously existed in spite of persistence of the thrill and murmur.

We are using at the present time the interposition of a rotometer in the proximal vein as a measure of the blood flow from the limb in which the fistula is placed. One of the first animals that we studied happened to be one which maintained a perfectly even blood pressure in a horizontal position, with the head elevated, and with the head down. In that animal the flow of blood from the limb was about 50 per cent greater when the limb was dependent than it was when the animal was horizontal, and about 50 per cent less when the limb was elevated than when it was in the horizontal position.

Most of our animals have had such marked changes in blood pressure, whether they were normally denervated or whether we had done bilateral carotid sinus denervation it has been difficult to interpret the results. Recently we have maintained a constant central blood pressure by placing a plastic cannula down the carotid into the arch of the aorta and by either withdrawing or giving blood through it as needed. If the central pressure is kept constant the femoral pressure in the normal leg is greater than the central pressure when the limb is dependent and it appears that the flow of blood from the fistulous limb is greater. When the limbs are elevated, the femoral pressure in the normal limb is less than the central pressure and the flow of blood seems to be less from the fistulous limb.

Using this method there are a number of other interesting things that are coming to light. We can show, quite definitely, that distal vein ligation increases the blood flow from the fistula into the proximal vein. I believe the same is true of distal arterial ligation. The blood flow is increased a great deal if the limb is sympathetically denervated. A number of other interesting problems have arisen with which I have had too little experience to permit discussion.

grafts appeared therefore, to be dilated (Fig 1). In some animals the apparent dilatation was greater than in the instance shown. It was our impression at the secondary operation, from thirteen days to fourteen months later

Fig 1



Fig *

Fig 1—Photograph made immediately after insertion of a 3.6 cm vein graft in the abdominal aorta of a dog.
Fig *—A 4 cm vein graft in the abdominal aorta of a dog fourteen months after operation.

The great advantage of vein grafts over artery grafts is that a suitable vein can be removed from the patient being operated upon without serious risk of circulatory insufficiency, whereas an artery of a size suitable for grafting cannot be removed safely. An artery graft must, therefore, have been secured in advance and properly stored. The difficulty of supply thus prevents the use of an artery graft except upon prearranged occasions or in conjunction with a constantly maintained artery bank.

Despite the experimental and clinical experience cited here, certain doubts existed in our minds concerning possible morphologic and functional alterations which might make vein grafts undesirable for clinical use. We were disturbed for example by the observation of Rose Hess and Welch¹⁸ that the arterial pressure appeared to be reduced in passing through a vein graft and by the occurrence of a false aneurysm in one of four vein grafts reported by Murray.¹⁹ Certain laboratory experiments were therefore undertaken and are herein described. In addition, two instances are reported of patients with the tetralogy of Fallot in whom vein grafts were used to bridge a defect between the subclavian artery and the pulmonary artery. The use of a vein graft for this purpose has not previously been reported to our knowledge.

EXPERIMENTAL STUDIES

Seventeen healthy mongrel dogs were selected for the experiments. Under intravenous sodium pentobarbital* anesthesia a right transverse abdominal incision was made and the inferior vena cava was exposed retroperitoneally. A segment of the vena cava from 10 to 46 cm in length, between the renal and iliac veins was excised and the lumbar veins and proximal and distal ends of the vena cava were ligated with silk. A segment of the adjacent abdominal aorta was then excised and replaced by the vena cava graft using the Carrel suture technique with 00000 silk. Transient mild swelling of the hindlimbs was observed in some animals but paralysis did not occur in any. Five dogs died during the postoperative period as the result of excessive anesthesia or respiratory complications but in none of the animals was there evidence of leakage or of thrombosis of the graft at autopsy or when sacrificed.

Femoral artery pulse p
Peterson Risman, and Dr
after operation and at th
tracings were taken under
operation or at a secondary operation performed up to fourteen months later,
the following additional studies were made (a) gross observations of the
appearance and function of the grafts and (b) aortography with 70 per cent
Diodrast injected proximal to the grafts. The animals were then sacrificed
The grafts were removed stained with hematoxylin and eosin and Weigert's
elastic stain and examined histologically

The diameter of the vena cava grafts was greater than that of the abdominal aorta in all instances. When the aortic clamps were removed the

Veterinary mebutal (pentobarbital Na) Abbott Laboratories North Chicago Ill Each cubic centimeter contains 10 gr of mebutal The dosage used was 0.4 cc per kilogram of body weight.

mation a progressive increase of fibrous tissue in all layers of the graft wall characteristically occurred. The thickening of the individual layers varied in different grafts and in different portions of the same graft. At thirteen



Fig. 5.—The vein graft shown by aortography in Fig. 4. This was the greatest dilatation of any graft in the series. It did not obstruct an artery in length 4 cm.

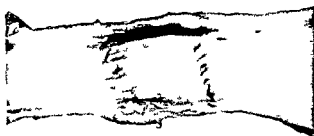


Fig. 6.—In the first vein graft there was little or no evidence of dilatation.

that there was a slight increase in the diameter of the longer grafts but not of the shorter grafts. There was no evidence of aneurysmal dilatation and all grafts functioned well. The characteristic appearance of a 40 cm. graft after fourteen months is shown in Fig. 2. The dilated appearance of the graft in Fig. 1 is shown by aortography in Fig. 3. The greatest dilatation observed is shown in an aortogram of another animal at fourteen months (Fig. 4). Serial aortograms in the same animal were not done.

Fig. 3

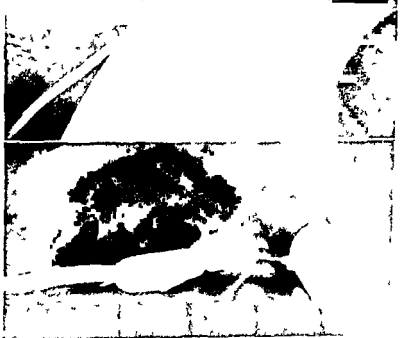


Fig. 4

Fig. 3—An aortogram of the ven graft shown in Fig. 1 before the dog was sacrificed.

Fig. 4—An aortogram showing the greatest dilatation of any of the ven grafts examined at fourteen months before the dog was sacrificed.

Following removal of the grafts the thickening of the graft wall was apparent on gross examination. Except for thickening, however, the grafts did not have the gross appearance of arteries (Figs. 5 and 6). The progressive thickening of the graft walls may be seen in sections examined without magnification (Fig. 7) and in photomicrographs (Fig. 8). On microscopic exam-

ination a progressive increase of fibrous tissue in all layers of the graft wall characteristically occurred. The thickening of the individual layers varied in different grafts and in different portions of the same graft. At thirteen

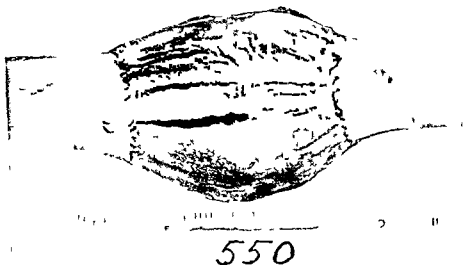


Fig. 5.—The vein graft shown by autography in Fig. 4. This was the greatest dilatation of any graft in the series. It did not suggest an aneurysm (length 4 cm).

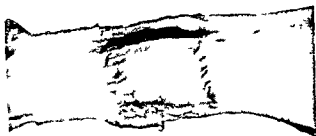


Fig. 6.—In this heart vein graft there was little or no evidence of dilatation.

days a cellular fibroplasia was observed (Fig 8, B). During ensuing months the fibrous tissue became denser and more acellular (Fig 8 C and D). In some instances smooth muscle fibers, sometimes in considerable amounts were seen in the intima. Hyaline intimal plaques occurred at the site of anastomosis.*



Fig 7.—Microscopic sections shown without magnification. A bit of the host wall is present in each end of the grafts in all in tan. The progressive thickening of the vein graft wall is apparent. A: 1 mm. lat. L: 10 days. C: 4 months. D: 4 months.

Femoral artery pulse pressure tracings taken immediately before and after operation and at six months.

Fig 9. The apparent alteration interpreted as being with

We are indebted to Dr. Robert C. Horn, Associate Professor of Surgical Pathology for examining and describing the microscopic sections.

†By Professor H. C. Bazett and L. H. Peterson of the Department of Physiology.

fects of the operative procedure. It appears certain that there were no significant differences between pulse pressure tracings taken before operation and tracings taken in the same animals from three to fourteen months after insertion of the vena cava grafts.

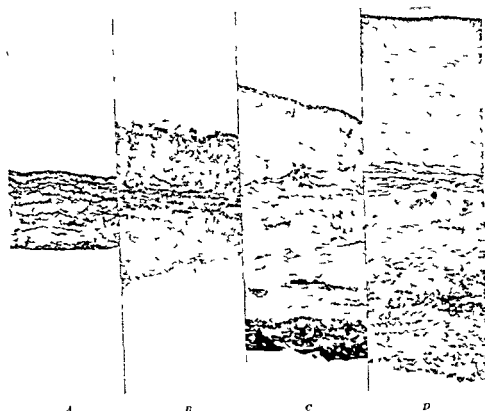


Fig. 8.—Photomicrographs of the vein grafts shown in Figure 7 (X9). A, Immediately; B, three days postoperatively; C, six months postoperatively; D, fourteen months postoperatively.

CLINICAL EFFICIENCY

The following case reports describe two patients with the tetralogy of Fallot in whom the subclavian artery could not be approximated to the pulmonary artery for an end to side or end to end anastomosis. A superficial femoral vein graft was used to bridge the defect in both instances.

CASE REPORTS

CASE 1—F. M., a 14-year-old boy, was admitted to the Hospital of the University of Pennsylvania on April 1, 1948, with a history of dyspnea and cyanosis since birth. The hemoglobin was 15.0 per cent and the hematocrit was 52 per cent. All studies were consistent with a diagnosis of the tetralogy of Fallot. The aortic arch was on the left. At operation on April 12, 1948, the right subclavian artery, after division just proximal to its branches, was found to be too short by at least 3.0 cm. for anastomosis to the right pulmonary artery. A 4.5 cm. graft was taken from the right superficial femoral vein and sutured between the end of the right subclavian and the side of the right pulmonary artery using the Carrel technique with 00000 silk. Following release of the clamp a strong thrill was palpable. After operation the patient's color was greatly improved and his progress was satisfactory until

the fifth postoperative day when he suddenly died. At postmortem examination a large embolus was found obstructing the stenotic pulmonary valve and infundibulum. The venous anastomoses were intact and the vein graft appeared to have been functioning well.

CASE 2—R. L., a 21-year-old man was first admitted to the Hospital of the University of Pennsylvania on Dec. 29, 1941. He had been cyanotic since birth. His activity had always been greatly limited and he could not walk more than a few feet without dyspnea. He was mentally retarded. All studies including cardiac catheterization were compatible with a diagnosis of the tetralogy of Fallot. The arterial oxygen saturation was 70 per cent, the hemoglobin 146 per cent, and the hematocrit 46 per cent. The arterial arch was on the left.

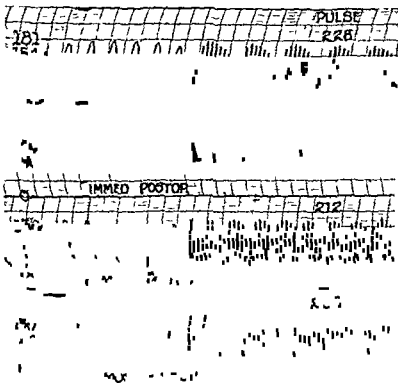


Fig. 3.—Representative pulse pressure tracings from the femoral artery of a dog in which a vein graft had been placed in the abdominal aorta.

On Jan. 16, 1942, exploration was done on the left side of the chest. The aortic arch was unusually high and had an uncoiled appearance. The left subclavian artery was only 1 inch long and could not be approximated to the left pulmonary artery for an end-to-side or end-to-end anastomosis. The left pulmonary artery could not be brought into apposition with the descending thoracic aorta which was somewhat lateral to its usual position without a great deal of tension. The attempt to establish a left to right shunt was therefore abandoned. The postoperative course was uneventful and the patient was discharged on Jan. 30, 1942.

Encouraged by the success of the vein graft in Case 1, we readmitted this patient to the hospital and on May 19, 1942, the second operation was performed. This time on the right, in order to avoid dissection of the aorta, one which was caused by the first operation on the left. The right subclavian artery was also very short and could not be approximated

to the right pulmonary artery. The defect was bridged by a superficial femoral vein graft 40 cm. long (Fig. 10). During the postoperative period there was a great improvement in the patient's color. When the patient was last seen, one year after operation, the arterial oxygen saturation was 94 per cent, a loud continuous murmur was heard to the right of the sternum and he stated that he could walk five miles without dyspnea.

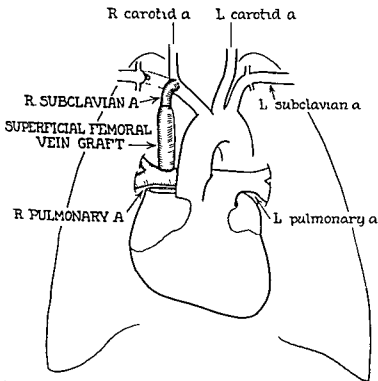


Fig. 10—Diagram of the situation of the superficial femoral vein graft between the right subclavian and pulmonary arteries in performing the Blalock operation for the tetralogy of Fallot.

COMMENT

The experiments described have increased our confidence in the use of vein grafts. From the functional standpoint there were no demonstrable changes in circulatory dynamics and using vessels of the size of the dog's aorta and inferior vena cava without anticoagulants thrombosis did not occur. From the morphologic standpoint the increase of fibrous tissue in the graft wall resulted in a structure which grossly and microscopically appeared to have considerable strength. Although some dilatation of the longer grafts occurred there was no evidence up to fourteen months that aneurysm formation was occurring.

SUMMARY

1. Inferior vena cava grafts were used to bridge defects of the abdominal aorta in dogs and were studied morphologically and functionally for fourteen months postoperatively.

2 Some dilatation of the grafts usually occurred but there was no evidence of aneurysm formation

3 Progressive thickening of the graft walls was observed Histologically, this was found to be due to an increase of fibrous tissue in all layers of the graft wall

4 The grafts appeared to function well in all instances when observed at a secondary operation prior to sacrifice

5 No changes in circulatory dynamics were demonstrable in femoral artery pulse pressure tracings up to fourteen months

6 In two patients with the tetralogy of Fallot superficial femoral vein grafts were used to bridge a defect between the subclavian artery and the pulmonary artery One patient died on the fifth day postoperatively from pulmonary embolism while the other has had an excellent functional result

REFERENCES

- 1 Carrel A and Morel L. Anastomose bout a bout de la jugulaire et de la carotide interne. *Lyons med* 99: 114, 1902
- 2 Carrel, A. and Guthrie C. C. Uniterminal and Biterminal Venous Transplantations. *Ann Surg* 100: 100, 1905
- 3 Watt J. B. The Transplantation of Blood Vessels. *Bull Johns Hopkins Hosp* 18: 15, 1905
- 4 Carrel A. Surgery of the Blood Vessels, *Bull Johns Hopkins Hosp* 18: 15, 1905
- 5 Guthrie C. C. Blood Vessel Surgery and Its Applications. London 191. Edward Arnold & Co.
- 6 Klotz O, Permar H. H. and Guthrie C. C. End Results of Arterial Transplants. *Ann Surg* 78: 305, 1923
- 7 Bernheim D. M. Surgery of the Vascular System Philadelphia 1913 J. P. Lippincott Company
- 8 Horsley J. S. Surgery of the Blood Vessels. St. Louis 1917. The C. V. Mosby Company
- 9 Bernheim B. M. Blood Vessel Surgery in the War. *Surg, Gynec & Obst* 30: 264, 1920
- 10 Blakemore A. H. Ford J. W. Jr. and Stehlo I. I. The Severed Primary Artery in the War Wound. I. A Suture Method of Bridging Arterial Defects. *Surgery* 12: 488, 1942
- 11 Ivor E. Beitrage zur Technik der Blutgefass- und Nervennaht mit Mittheilungen uiber die Verwendungs eines resorbirbaren Metalles in der Chirurgie. *Arch f klin Chir* 62: 67, 1900
- 12 Hopfner F. Gefassnaht (Gefass-Transplantation und Reimplantation von Blutgefassen). *Monatsschr Chir* 70: 417, 1903
- 13 Hopfner F. The Arteries in World War II. *Ann Surg* 138: 1, 1924
- 14 Fontaine A. Quoted by F. A. Simeone. Personal Communication
- 15 Carrel A. Latent Life of Arteries. *Exper Med* 12: 469, 1910
- 16 (a) Carrel A. and Guthrie C. C. Preliminary Observations on the Treatment of Certain Cardiovascular Diseases. *Ann Surg* 100: 100, 1905
- 17 (b) Carrel A. and Guthrie C. C. A Method of Preservation and Transplantation of Blood Vessels. *Ann Surg* 100: 100, 1905
- 18 Rost R. Injuries of the Extremities in World War I. *Surg, Gynec & Obst* 30: 264, 1920
- 19 Murry J. A. A New Method for Recording Arterial Pulse in Man. *Am Heart J* 37: 771, 1949
- 20 Peterson J. H., Risman G. C., and Dripps R. D. A New Method for Recording Arterial Pulse in Man. *Am Heart J* 37: 771, 1949

DISCUSSION

DR ROBERT GROSS—For a period of several years we have been interested in studying the effects of transferring large arteries from one animal to another. Our fellows Dr Pearle Dr Rheinlander and Dr Bill have transferred aortic segments from one dog to another in a series of more than 200 experiments.

Some of these grafts were fresh, others were preserved in various ways. I cannot summarize all of this material here, but we can quickly say that many of the methods of preservation are unsatisfactory. There are however methods of preserving grafts for periods of up to six weeks so that they can be transferred from one animal to another with a high degree of success.

With this laboratory background we felt justified in trying some grafts from one human being to another in sixteen patients various gaps in large vessels of the arterial system within the chest have been bridged by the use of preserved material which had been obtained from people who had died in accidents. Three of the six patients died within a few days from totally unrelated causes. The remaining patients are alive for periods of several months to as long as one and one half years. To the present all of these grafts have remained open as far as we can tell. We feel justified in saying that for the period of observation (up to one and one half years) these grafts apparently act as very effective channels. What is going to happen over a longer span of time is unknown.

I think this is a very valuable contribution which Dr Johnson and his co-workers have made because it emphasizes the possibility of using veins from the same person to bridge gaps of certain arteries other than the aorta. The method is especially attractive because the use of a graft from the same person obviates the risk of any antibody reaction which might occur when tissue is used from another individual.

I would like to emphasize and I am sure that Dr Johnson and his associates will agree with me that in bridging a gap in arteries the best way to establish a satisfactory channel is to mobilize (if possible) the ends of the vessels and get them together by direct union. Failing that, the technique here described of using a vein graft from the same individual is probably our next best method. As a last resort the use of a graft which has been kept in some form of a vessel bank will probably help the surgeon out of his difficulty.

DR NORMAN E. FREEMAN—I am very happy to have this opportunity of discussing the splendid paper which Dr Johnson and his associates have presented. In my limited experience with autogenous vein graft, not only has the circulation been satisfactorily re-established but over the course of time the transplanted vein has appeared to constrict so as to approach more and more the caliber of the artery into which the graft has been inserted.

I should like to show the arteriograms on one patient who had a segment of upper femoral vein transplanted to bridge the gap in the popliteal artery after resection of a large aneurysm. The first arteriogram taken three weeks after operation shows a considerable dilatation of the venous segment. The second arteriogram taken fifteen months after operation shows the venous segment reduced in caliber so as to be indistinguishable from the artery.

I should like to comment on the use of homologous grafts. Experiments performed with Dr A. F. Scherter in the Harrison Department of Surgical Research of the University of Pennsylvania's Medical School demonstrated an individual specificity of serum or plasma in dogs. Serum or plasma obtained from the donor animal was injected intracutaneously into a recipient dog which had previously been given an intravenous injection of T.B. A wheal formed which was stained blue, due to the passage of the recipient's own plasma into the injected area. Serum or plasma obtained from the recipient did not produce any reaction. From these observations it was concluded that an individual specificity was present even in such undifferentiated biologic material as serum or plasma.

The blood vessel wall contains smooth muscle and elastic tissue both highly differentiated and essential components. If the components of the homologous graft were to be replaced by fibrous scar tissue, it would appear likely that dilatation and ultimately aneurysmal forma-

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REFERENCES

- 1 Carrel A and Morel L. Anastomose bout a bout de la jugulaire et de la carotide interne. Lyon méd 99 114 1902
- 2 Carrel A and Morel L. Pterminal Venous Transplantation
- 3 Carrel A. Implantation and Transplantation of Arteries. J. Exp. Med. 1907
- 4 Carrel A. Surgery of the Blood Vessels. Bull. Johns Hopkins Hosp 18 19 1907
- 5 Guthrie C C. Blood Vessel Surgery and Its Applications. London 1911. Edward Arnold & Co
- 6 Klotz O, Permar H H and Guthrie C C. Final Results of Arterial Transplants. Ann Surg 78 30 1923
- 7 Bernheim B M. Surgery of the Vascular System. Philadelphia 1913. J. B. Lippincott Company
- 8 Hordey J S. Surgery of the Blood Vessels. St. Louis 1916. The C. V. Mosby Company
- 9 Burnheim, B. M. Blood Vessel Surgery in the War. Surg. Gynec. & Obst. 30 564 1920
- 10 Blakemore A H, Lord J W Jr and Stefkó P I. The Severed Primary Artery in the War Wounded. A Non-suture Method of Fixing Arterial Defect. SURGERY 12 488 1949
- 11 Iayer L. Beiträge zur Technik der Blutgefäß- und Nervenennaht mit Mittheilungen über die Verwendung eines resorbirbaren Metalles in der Chirurgie. Arch. f. klin. Chir. 62 67 1900
- 12 Hopfner F. Ueber Gefäßennaht, Gefäßtransplantation und Reimplantation von amputirten Extremitäten. Arch. f. klin. Chir. 70 417 1909
- 13 DeBakey, M. F. and Simeone F. A. Battle Injuries of the Arteries in World War II. Ann. Surg. 123 534 1946
- 14 Blakemore A H. Restorative Endoaneurysmorrhaphy by Vein Graft Inlay. Tr. Am. S. A. 65 411 1944
- 15 Fontana
- 16 Carr
- 17 (a) Primary Obstruction of Certain Carotids
- (b) Preservation and Replantation of Extremities in
- 18 Roubicek A, Heister. Battle Casualties. Ann. Surg. 123 161 1946
- 19 Murray G. Heparin in Thrombosis and Blood Vessel Surgery. Surg. Gynec. & Obst. 72 344 1941
- 20 Peterson L H, Risman G C and Driggs R D. A New Method for Reordering and a Concept for Utilizing Arterial Poles in Man. Am. Heart J. 37 71, 1949

COMPLICATIONS OF ANTICOAGULANT THERAPY

GEORGE D. LEE, M.D. AND ROBERT M. LEE, M.D. MIAMI, FLA.

THE unlimited enthusiasm of Allen Barker and Hines^{1,2} regarding the therapeutic value of the anticoagulant Dicumarol in the treatment of pathologic intravascular thrombosis has permeated to the byways of medical practice with the disastrous results which they themselves seemed to fear when they said "The best method of preventing hemorrhage is to use dicumarol expertly."

In 1943 DeBakey³ raised a note of caution against the promiscuous use of this toxic substance with the comment that "a restatement of facts is frequently necessary to dispel the fog of enthusiasm and thus permit a clear discernment of objectives." To substantiate this he called attention to the work of Zava⁴ who reported over 6,000 major surgical cases without a single embolic complication. He also commented upon the report of 4,410 consecutive operations performed at the Charity Hospital in New Orleans in which there were three (0.06 per cent) cases of postoperative embolism. Such statistics certainly compare most favorably with those reported by the Mayo Clinic group who had used anticoagulants with such enthusiasm. Their enthusiasm is difficult to understand when one observes that even in their expert hands there has been an incidence of hemorrhagic complications of 8.7 per cent. They observed 'slight bleeding' in patients in 5.3 per cent of their series and 3.2 per cent had severe bleeding requiring transfusions. In addition to this they reported five fatal hemorrhages which occurred while Dicumarol was being administered. In 1945 DeBakey³ pointed out that much safer procedures, if carried out with the same diligence, might accomplish the same desirable reduction in mortality from postoperative thromboembolism without subjecting surgical patients to the hazards of this poison. Since that time reports of tragic results have been appearing in the medical literature with disturbing regularity.⁵⁻⁷ The recent publication of Duff and Shull⁸ in which reports of twenty three deaths resulting from Dicumarol poisoning were collected and reviewed causes one to speculate upon the actual number of serious and fatal complications which are the results of this form of therapy in our smaller hospitals and in general home practice. Certainly very few of them are being reported and many of them are not even recognized.

The recent report of Wise, Locker and Lumbel⁹ is particularly impressive because even though they concluded from their analysis of 12,554 surgical cases that the value of anticoagulants in the prevention of postoperative thromboembolic complications is mathematically probable they conscientiously curbed their enthusiasm with such statements as "One must bear in mind that the use of an induced controlled hemorrhagic state to combat a transitory physiological clotting tendency is potentially hazardous by its very nature" and "The effort necessary to surmount the difficulties to pursue

Read at the third annual meeting of the Society for Vascular Surgery, Atlantic City, N. J. June 5, 1949.

tions would occur under the influence of the continued high arterial pressure. Dr. Johnson and his co-workers are to be congratulated for their careful observation on the use of autogenous vein grafts.

DR. HARRIS B. SHUMACKER.—I was very much interested to hear the results of Dr. Johnson's studies, and I think the studies that he and his associates have made are very valuable indeed.

We have had a fairly small but quite successful experience with the use of autogenous veins as free grafts to bridge arterial defects in man in the course of operating for aneurysms and arteriovenous fistula.

About two years ago, my associates and I decided to do two things—first to reinvestigate the problem of using venous transplants to the abdominal aorta in experimental animals, second to review the entire literature with regard to the effects in which there was recorded a histologic description of the graft.

A great many people worked upon this problem and the results recorded in the older literature are very informative. In general we had the feeling after reviewing this work that it could be said that these transplants to arterial defects were functionally satisfactory but that histologically they varied a great deal according to the type of transplant. In general there seemed to be justification for the assumption that only autogenous venous transplants survived as living structure and that homologous and heterogenous grafts were replaced by fibrous tissue from the host, regardless of whether they were fresh or were fixed in some medium such as formalin or whether they were preserved solely by refrigeration.

In our own studies we used fresh preserved and fixed autogenous homologous and heterogenous veins as transplants. Usually they seemed to function well during the period of observation which in our cases was not longer than ten months but histologically they varied a great deal. Whether the histologic appearance of these grafts is of real importance, I do not know, but the autogenous venous grafts seemed to survive as living structure and from our experience we agree with others that the other types of grafts undergo degeneration and fibrous reinforcement. It is hard to tell them apart grossly or functionally.

It seems to me that these problems are worthy of further investigation and we are trying to study these matters at the present time. First what are the very long term results? In the older literature there is one eleven year old graft described by Guthrie, but I do not believe we have evidence showing that it is still functional. Second, do these grafts grow? I do not believe we have evidence showing that they do in any animals such as

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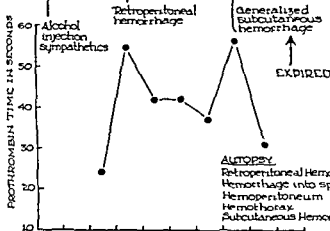
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It seems to me that these problems are worthy of further investigation, and we are trying to study these matters at the present time. First what are the very long term results? In the older literature, there is one eleven-year-old graft described by Guthrie but generally grafts have been studied over only short intervals. Second do these grafts grow with the growing animal? Up to the present time I do not believe we have evidence along this line but it should be easy to obtain in a relatively short time using animals such as pigs which grow rapidly.

CASE I (J.C.H.) WM 68 years of age EMBOLUS Abdominal Aorta

DAY of THERAPY 1 2 3 4 5 6 7 8 9 10



AUTOPSY

Retroperitoneal Hemorrhage
Hemorrhage into spleen
Hemoperitoneum
Hemothorax
Subcutaneous Hemorrhage

DICUMAROL_{mg} 350 200 200

HEPARIN_{mg} 50 50

BLOOD_{cc}

500 500 500

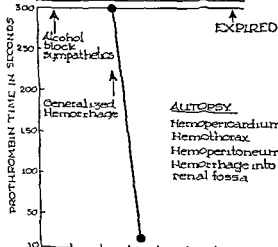
VITAMIN K_{mg}

100 200 200

Fig. 1

CASE II (E.S.C.) WF 63 years of age EMBOLUS Left common femoral artery

DAY of THERAPY 1 2 3 4 5 6 7



AUTOPSY

Hemopericardium
Hemothorax
Hemoperitoneum
Hemorrhage into renal fossa

DICUMAROL_{mg} 300 200

HEPARIN_{mg} 30 45 30

BLOOD_{cc}

500 500 500

VITAMIN K_{mg}

such a course of prophylaxis to reduce an already relatively small incidence of fatal and non fatal thrombo embolic complications" may not be worthwhile. Evans and Dicker¹¹ seemed to be in the same frame of mind when they concluded their survey of 45 000 major surgical cases at the Lister Clinic in which they encountered fifty two fatal pulmonary emboli by commenting that one of their hospitals, in which the nursing staff was trained to insist upon "bicycle exercises" in all postoperative patients, had only one third as many postoperative thromboembolic complications as another hospital which did not pay the same attention to this simple and safe prophylactic procedure.

When one studies the excellent survey of the present uncertain status of laboratory procedures for determining the effect of Dicumarol on prothrombin levels which has been published recently by Alexander deVries and Goldstein¹ and heeds their warning that "Present laboratory techniques for prothrombin estimation have their limitations, and failure to recognize them may prevent accurate diagnosis obstruct effective therapy and even invite disaster" one may justifiably speculate upon the possibility that the enthusiastic reports of the Mayo Clinic group⁴ and those of Wright and his co workers¹² may actually cause more deaths than they prevent when their enthusiasm permeates to the outposts of medical practice.

In the early days of Dicumarol, before the drug had been released for general distribution, we experimented with it, after two minor hemorrhagic complications, we were glad to give our supply of the drug to more enthusiastic members of our hospital's medical staff and observe its use for the side lines. The following cases have come to our attention, without any conscious effort on our part to conduct a careful investigation of complications of anti coagulant therapy in our two hospitals and we have reason to believe that they represent only a small fraction of the complications which have occurred in our community in recent years.

CASE REPORTS

CASE I (Jackson Hospital No 6813 Autopsy No 199/44) —J C H a 68 year old white man, was admitted Nov 4 1944 with a complaint that four hours prior to admission he experienced a severe epigastric pain radiating through to the back and down both legs. Within a few minutes after the onset both lower extremities became paralyzed. On admission both lower extremities were cyanotic cold and pulseless and the lower abdomen was extremely tender. A diagnosis of dissecting aneurysm versus embolic occlusion of the lower abdominal aorta was made and a bilateral alcoholic injection of the lumbar sympathetic trunk was done. As soon as this was completed 50 mg of heparin were injected intravenously and 300 mg of Dicumarol were given by mouth. There was marked improvement in circulation to the feet and complete relief of pain following the sympathetic interruption and the following morning the patient could move the toes of both feet. Anticoagulant therapy was supervised by a medical man who was especially interested in this type of therapy and at all times the patient seemed to be well controlled. On Nov 8, 1944 four days after admission, the patient complained of severe pain in the right lower abdominal quadrant and there was clinical evidence of shock. Whole blood and vitamin K were given. The next day there were numerous areas of subcutaneous hemorrhage and the circulation to the lower extremities was entirely shut off. In spite of four tran fusions and large quantities of vitamin K hemorrhage continued. The patient died on Nov 13, 1944.

femoral artery below the profunda branch. He was admitted to the hospital on April 27 1948 five days after the occlusion with a cramping painful left lower extremity in which there was no palpable pulsation except in the femoral artery at the foot which was normal. Through poor surgical judgment, an attempt at embolectomy was carried out under painful

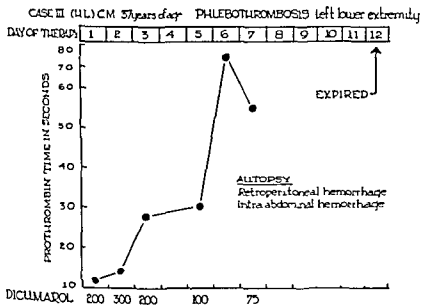


FIG. 3

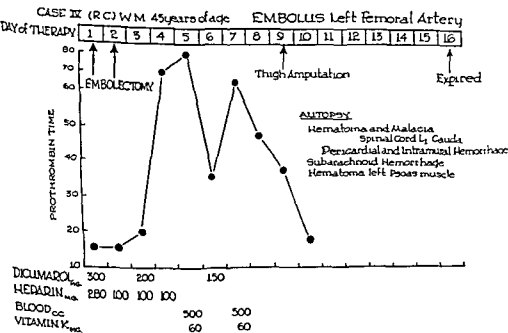


FIG. 4

Autopsy findings were (1) dissecting aneurysm of lower aorta (2) bilateral profuse retroperitoneal hemorrhage at site of sympathetic block, (3) profuse parenchymatous hemorrhage in spleen, (4) hemoperitoneum, (5) hemothorax (6) multiple subcutaneous hemorrhage (7) advanced atheromatosis, (8) arterio sclerosis of kidneys, (9) hypertrophy of prostate

This man died as a direct result of Dicumarol poisoning. Before hemorrhage started, it appeared that the extremities were to be saved.

CASE II (Jackson Hospital No 85391)—F S C a 63 year old white woman was admitted to the hospital on March 29 1945, with uterine bleeding. On March 30 1945 a total hysterectomy and right oophorectomy were carried out because of the possibility of carcinoma of the fundus of the uterus. The patient had an uneventful postoperative course for the first forty eight hours and then experienced a sudden severe pain in the left thigh and lower leg. The extremity became pale and pulseless. A diagnosis of embolus to the common femoral artery was made and within three hours an alcoholic injection of the left lumbar sympathetic trunk was carried out. Two hours later anticoagulant therapy was instituted (Fig 2). For the next forty eight hours the patient had a very stormy course as ischemic gangrene developed from the knee down. On the third day of anticoagulant therapy the patient took a very definite turn for the worse, there was marked abdominal distention and vomiting of blood as well as extensive ecchymosis in the flank. The anticoagulants were stopped, and she received 500 cc of whole blood. At that time the prothrombin time was 300 seconds. The following morning the prothrombin time was 18 seconds, but the patient continued to bleed, in spite of large doses of vitamin K. The following day an additional 500 cc of whole blood was given. She continued to show evidence of internal hemorrhage and died six days after anticoagulants were begun and three days after they were discontinued. Autopsy revealed (1) diffuse hemorrhage into the pericardium, both renal fossae both psoas muscles (region of alcohol injections) peritoneal cavity, and multiple subcutaneous hemorrhages, (2) thrombosis of left femoral artery, due to advanced arteriosclerosis and dissecting aneurysm, (3) rheumatic heart disease, (4) advanced atheromatosis (5) generalized secondary anemia.

This woman lost her life because of anticoagulant therapy. Undoubtedly prothrombin time determination should have been made during the first forty eight hours, but it is interesting to observe that the prothrombin time reached five minutes on what is accepted as moderate dosage and it is interesting to observe that she continued to bleed after the time returned to normal. This and the preceding case convinced us that anticoagulant therapy and paravertebral sympathetic block should never be combined. The same complication occurred in Case 3.

CASE III (Dade County Hospital No 48010)—H L a colored man aged 31 year was

retroperitoneal hemorrhage at sites of sympathetic blocks (undoubtedly emphysema); hemorrhage of lesser degree into kidneys liver and adrenals with a final interesting comment by the pathologist: "evidence of necrosis and loss of striation due to lack of blood flow into the precapillaries and the lack of red blood corpuscles." It was not

CASE IV (Jackson Hospital No 47020)—R C a white man aged 45 years had been in good health until April 1948 when he suddenly developed an occlusion of the left

was stopped. On March 29 1949, the patient had another severe attack of epigastric pain and went into shock. She was admitted to the hospital where supportive treatment was given. At that time the prothrombin time was reported as 40 seconds (control 13 seconds). The patient lapsed into a deep coma and died on April 1, 1949. Autopsy revealed (1) massive hemorrhage into peritoneum, liver, kidneys, pleural cavities and into the pericardial cavity.

Apparently this woman had been well standardized on Dicumarol for nine months when she suddenly developed severe generalized hemorrhages, with no change in the medication routine.

CASE VI (Jackson Hospital No 36493) — J. L., a white man aged 48 years had had recurring bouts of thrombophlebitis of the superficial veins of the left lower extremity for two years. Two weeks before admission to the hospital he developed a red tender area on the left long saphenous at the knee and experienced a dull sharp pain in the right side of the chest. The chest pain and the phlebitis seemed to be improving until the day of admission, at which time he experienced the same sudden severe pain in the left side of the chest. He was admitted to the hospital on Nov. 6, 1947, and a diagnosis of thrombophlebitis of the left

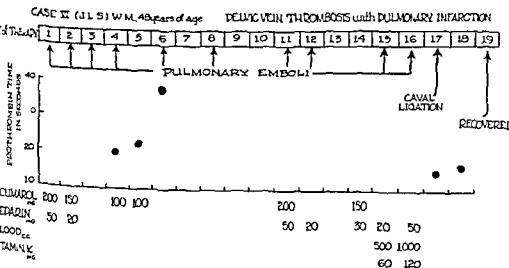


FIG. 6

long saphenous at the knee with pulmonary emboli was made. He was given 200 mg of Dicumarol and 50 mg of heparin. On the following day he was given 150 mg of Dicumarol and 20 mg of heparin. Two days later Nov 8 1947 the prothrombin time was 40 seconds. He experienced another severe pulmonary embolus at this time and the entire left lower extremity became swollen. On this day and the following day 100 mg of Dicumarol were given and on Nov 10 1947, the prothrombin time was 89 seconds. On Nov 23 1947 the entire right lower extremity became swollen and he was given 200 mg of Dicumarol. The following day he experienced a severe pulmonary embolus. On Nov 23 1947 an additional 100 mg of Dicumarol were given and that evening another lower of small pulmonary emboli occurred. On Nov 23 1947, we saw the patient in consultation and made a diagnosis of thrombosis of the lower vena cava. Fresh whole blood 500 cc was given and large quantities of vitamin K were administered. The following morning the vena cava was ligated and sectioned about 5 cm above the bifurcation. Fresh whole blood 1000 cc was given during surgery. No further emboli occurred and the patient made an uneventful recovery. He now has a slight evening edema of the ankles which is easily controlled by the use of elastic stockings.

and then. This patient was then subjected to the additional unnecessary trauma of a paravertebral sympathetic injection of procaine while he was still under the influence of spinal anesthesia. During the twelve hours immediately after surgery he received 300 mg of Dicumarol and 240 mg of heparin. The patient went into shock. The foot remained cyanotic and pulseless, but the pain was relieved because a complete motor and sensory paralysis had developed from the umbilicus down. Twenty-four hours after the first surgery he was operated upon again and another attempt at embolectomy was made. This time he required no more than 1 cc of procaine. At the same time an alcoholic injection into the region of the left foot muscle was carried out, in an attempt to interrupt the sympathetic innervation to the lower extremity. On May 2, 1948, hemorrhage into the spinal cord was recognized for the first time, and anticoagulant therapy was discontinued. He was given 60 mg of vitamin K and an exploratory spinal puncture revealed dark red blood. On May 4, 1948, a mid-thigh amputation was carried out, following this he developed infection in the amputation site, infection of the urinary tract and a decubitus ulcer. He died on May 10, 1948. Autopsy revealed: (1) a hematoma and rupture of the spinal cord from the first lumbar to the caudal equina; (2) intramural thrombus in the right side of the heart; (3) ecthyma of the left foot and rhomboid muscles; (4) emboli of left femoral artery; (5) generalized arterio-sclerosis.

This man lost his life as the result of a massive hematoma into his cord at the site of spinal puncture.

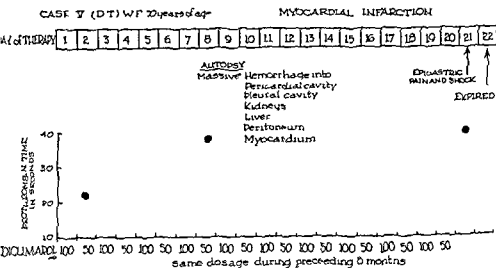


Fig.

CASE V (S. Francis Hospital No. 5894) - D.T. a white woman aged 40 years had been known to have cardiovascular disease for twenty-five years. In July 1949 she was admitted to a Washington D.C. hospital with cerebral thrombosis and at that time she was placed on heparin and eventually remained on anticoagulant therapy from that time on. She seemed to be well stabilized on alternating daily doses of 100 mg and 50 mg of Dicumarol. She came to St. Francis during January 1950 to consult as she was continued on alternating doses of 100 mg and 50 mg of Dicumarol at daily intervals. Weekly prothrombin determinations were advised but were refused by the patient who felt that they were unnecessary. On Jan. 15, 1950, 70 per cent of normal was reported and on Jan. 22, 35 per cent of normal. On Jan. 23, 1950, she had chest and precordial pain. The Dicumarol

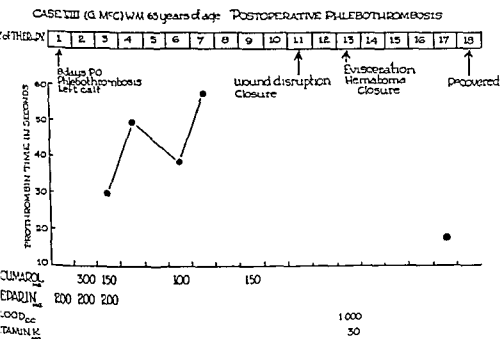


Fig 4

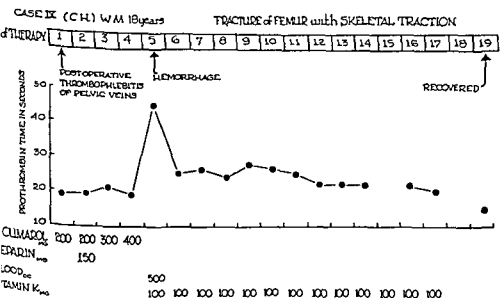
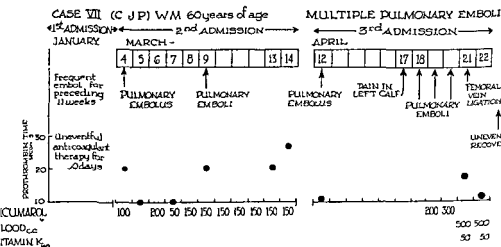


Fig 5

It is true that this man's anticoagulant therapy was poorly supervised but even so, he did experience almost daily showers of pulmonary emboli while on fairly adequate doses of the drug. During this time a trivial local phlebitis which could have been rendered harmless by a simple saphenous ligation, extended into the femoral and iliac veins and up into the lower vena cava necessitating a hazardous and disabling surgical procedure.

CASE VII (St Francis Hospital)—C. J. P. a white man aged 60 years during September 1948, developed severe pleuritic type of pain over the right side of the chest, with hemoptysis. A diagnosis of virus pneumonia was made and he was treated with penicillin. He continued to have attacks of severe pain and hemoptysis and therefore was placed on anticoagulant therapy for 4½ weeks. He made a gradual recovery and on Feb. 4 1949 was discharged from the Harkness Pavilion and sent to Miami to recuperate. On March 4 1949 he experienced a sudden severe pain in the right side of the chest and coughed blood tinged sputum. A diagnosis of pulmonary embolus from an unknown source was made and anticoagulant therapy was resumed. On March 17, 1949 while on adequate Dicumarol therapy he complained for the first time of pain in the left calf. This cleared in a few days and he



Fig

was discharged from the St Francis Hospital and anticoagulant therapy was discontinued on April 6 1949. On April 18 1949 while straining at stool the patient collapsed. A diagnosis of right pulmonary infarction was made and a swelling and tenderness of the left calf was noted. A phlebogram of the left saphenofemoral venous junction was carried out. The patient died in a few months. This was a very severe case of thromboembolism. In even months he feels

w 11

This man's first two attacks of thromboembolism may have been arrested by anticoagulants but the course of this case raises the interesting question: When should anticoagulant therapy be discontinued?

CASE VIII (Jackson Hospital)—G. McC. a white man aged 60 years on Feb. 19 1949 underwent a subtotal gastric resection because of a prepyloric lesion which later was found to be a benign ulcer. The postoperative course was entirely satisfactory until Feb. 27 1949 (eight days postoperative), when he developed phlebotrombosis of the left lower extremity

CONCLUSIONS

Reliable laboratory procedures for the estimation of prothrombin levels are not available

Dicumarol is a hazardous therapeutic agent at best and when it is employed by inexperienced or inattentive physicians it rapidly assumes the role of a fatal poison

Dicumarol therapy in postoperative patients may cause sudden, severe and even fatal hemorrhage even when carefully controlled by experts

There is no justification for the employment of anticoagulant therapy in cases of phlebotrombosis and thrombophlebitis limited to the lower extremity below the groin because proper vein interruption is a more certain, much safer, quicker, and much less expensive method for the control of this condition

The prophylactic use of anticoagulants in postoperative patients is fraught with hazards and its general use probably will lead to an increase in mortality rates, as well as medicolegal complications. Correct bed posture and properly supervised exercises will accomplish the same prophylactic results safely and economically

REFERENCES

- 1 Allen F V, Parker N W and Waugh J M. Inhibition From Spoiled Sweet Clover (33 Methylene Bis) (4-hydroxycoumarin) Which Prolongs Coagulation and Prothrombin Time of Blood. *Clinical Study* J A M A 120: 1609 1942
- 2 Allen F V, Hines I A, Kvale W I and Barker N W. The Use of Dicumarol as an Anticoagulant. Experience in 2307 Cases. *Ann Int Med* 27: 371 1941
- 3 Barker Nelson W. The Use of Dicumarol in Surgery. *Minnesota Med* 27: 102 1944
- 4 Parker N W, Hines I A Jr, Kvale W I and Allen F V. Dicumarol. *N Y Med J* 3: 634 1944
- 5 DeBakey M E. - - - - - cular Thrombosis
- 6 Cahan A. - - - - - rt of a Case
- 7 Schlesinger A. - - - - - cumarol Therapy
- 8 Thorpe J. - - - - - c, *Lancet* 2: 40
- 9 Dr. L F and Shull W H. Fatal Hemorrhage in Dicumarol Poisoning. *J A M A* 193: 107, 1949
- 10 Wise W D. *Lock* - - - - - arol Prophylaxis v A Four Year
- 11 Franz James. - - - - - Pulmonary Em-
bolism—
1947
Med 236: 30
- 12 Alexander Benjamin, deVries Andre and Goldstein Robert. Prothrombin. A Critique of Methods for Its Determination and Their Clinical Significance. *N England J Med* 240: 403 1949
- 13 Wright L S. *Medicine* - - - - - Report of the Committee for Evaluation of Coronary Thrombosis With Myocardial
- 14 Lilly C. - - - - - Sympathetic Trunk J A M A 128: 49

DISCUSSION

DR ARTHUR W ALLEN—Dr Carlson of Chicago once made a statement which interested me very much. He said in effect: There are three types of discussions, two of

Anticoagulants were started. On March 9, 1949 (tenth day of anticoagulant therapy and twentieth postoperative day), there was a disruption of the wound and a massive subcutaneous hematoma. Anticoagulant therapy was terminated. On March 11, 1949, the wound disrupted again. A large amount of liquid blood was removed from the peritoneal cavity and the wound was closed with interrupted wire. The patient made a stormy but satisfactory recovery.

CASE IX (St Francis Hospital)—C H, a white man aged 18 years suffered a fracture of the neck of the right femur, necessitating open reduction and the installation of a Steinmann pin. A thrombophlebitis developed two weeks later and anticoagulant therapy was instituted. Four days later the right lower extremity from the level of the Steinmann pin downward became swollen, cold, and dark blue or black in color. This change occurred overnight and was associated with severe pain. Careful examination revealed that massive subcutaneous hemorrhage had occurred at the site of the pin and had infiltrated all the subcutaneous tissues down to the tips of the toes. The first appearance was that of massive gangrene.

The anticoagulant therapy was discontinued by use of fresh whole blood and vitamin K, and the patient made a gradual recovery.

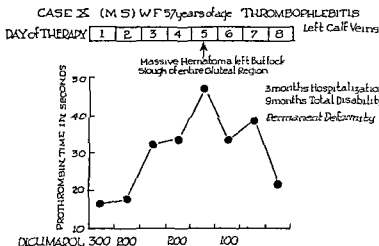


Fig. 10

CASE X—M S a white woman, aged fifty-nine years was admitted to the hospital with a diagnosis of thrombophlebitis of the deep veins of the left leg. She was placed on bed rest and started on Dicumarol therapy as indicated on Fig. 10. Five days after the beginning of anticoagulant therapy she developed a massive hematoma in the left gluteal region in spite of a recent intramuscular injection of penicillin. In spite of this she was con-

she required four months of hospitalization and numerous dressings before healing was finally accomplished with marked scarring and deformity and some permanent discomfort.

SUMMARY

Five previously unreported deaths and five serious postoperative complications resulting from anticoagulant therapy are described.

may from 10 per cent of normal up to normal. I am sure that this illustrates one of our greatest difficulties. We have seen some tragic results from the misuse of this drug in addition to the experiences described here. I am sure that you will agree with me that Dr. Lilly has brought to us a very timely and convincing communication.

DR. A. WILBURN DILLIPE—I do not know whether a medical man dare get up in front of this group and put in a word, but I would like to compliment Dr. Lilly on his excellent presentation of the case patients because he calls to our attention the necessity of being on guard in the use of these potent drugs.

I believe we should not be alarmed by these serious complications but be guided rather by the successes compared to the failures. When one looks back on the early days of the use of digitalis and of the sulfonamide he can many deaths attributed to them.

As far as we know there have been about 60 deaths from the use of anticoagulant in the last 10 years. Of course there may have been others that have not been reported. If one takes in these deaths against the individuals who have been saved from anticoagulant therapy, I believe we have sound ground for continued anticoagulant therapy.

I agree heartily with the other speakers who have opened this discussion that we must have better anticoagulant after ones if they are developed. This may not be possible since any substance that prevents the clotting of blood has a real danger. We must also have better means of checking their action than we have today. Papers like Dr. Lilly's play a most valuable part in instructing the general practitioner and warning him of the dangers of these drugs.

If one takes a series like Brantley's from Baltimore where for instance the laboratory is set up for almost perfect control of prothrombin activity, one gets another outlook. He has given Dicumarol to thousands of post partum patients. As reported yesterday afternoon there were no serious hemorrhages and no fatalities. It is evident that one can use these anticoagulants in a large series of patients without trouble.

But until we evaluate the successes against the failures we will not be able to place these therapeutic agents in their proper places.

DR. ALTON OCHSNER—We too have feared anticoagulant but have felt that they might be used in individuals who are potential thromboses, provided that one could determine who these individuals are. On the other hand we believe that the routine use of anticoagulants is extremely hazardous as Dr. Lilly has emphasized.

For the past two years Dr. Kay working in our laboratory has shown that intravenous thrombosis is of the phlebotrombotic type, dependent upon the relative proportion of antithrombin and prothrombin and that if the antithrombin is low enough a venous clot will occur even though the prothrombin content may also be low. The prothrombin determination alone does not give any indication concerning the thrombotic tendency. It is possible to determine accurately which patients are likely to develop a venous thrombosis by daily determinations of prothrombin and antithrombin. We have demonstrated that following an operative procedure all patients have a decrease in the normal antithrombin content, but that normally the antithrombin content regains its normal level within a period of four to five days. However, the patient who will develop a clot has a progressive fall in the antithrombin content until the clot occurs, at which time the antithrombin content of the blood is extremely low. We have observed a number of these patients watching their antithrombin level fall until a thrombus developed and then we have operated upon them and have proved that a thrombus was present. By ligation of the vein proximal to the clot we have prevented development of the thrombus.

Although the patient with a progressive fall in antithrombin content following injury is a potential thrombosis, it is possible to prevent venous thrombosis by the administration of antithrombin. We have found that alpha tocopherol is an efficient antithrombin and we believe it is probably one of the principal antithrombins in the blood. By supplying antithrombin in the form of alpha tocopherol the deficiency in antithrombin is corrected and a clot is prevented. The great advantage of using antithrombin in the form of alpha tocopherol is that although the thrombotic tendency is overcome, a hemorrhagic tendency is not produced such as occurs when anticoagulants, such as heparin or Dicumarol, are used.

them are bad. One of the bad ones is the man who repeats the paper that has just been presented, and the second is one who presents another paper that may not have too much bearing on the subject.

With the risk that you may criticize me in this second category, I will present to you some of the experience which we have had with the complications of anticoagulant therapy at the Massachusetts General Hospital.

This experience dates back a good many years, in fact since heparin was first made available and this drug was used quite commonly in various conditions when it was thought that it was proper to increase the coagulation time of blood.

The cardiac service under the direction of Dr. Paul D. White when the sulfonamide drugs first became available thought that perhaps they could benefit patients with acute and subacute bacterial endocarditis by the combined use of sulfonamide drug and heparin. Their experience in some twenty-eight cases convinced them to believe that heparin was too dangerous to use particularly in the older age group since too many of these people developed cerebral hemorrhage during the treatment.

We also observed two instances of cerebral hemorrhage in elderly individuals who were treated with heparin for peripheral arterial sclerosis. This made us cautious about the prophylactic use of anticoagulants so that when we began using Dicumarol we started with great care.

(Sibley) We soon found during our experimental series that people reacted very differently to this drug. Quite often a very small dose of Dicumarol gave a very marked elevation of the prothrombin time, while other patients appeared to be very resistant or tolerant of the drug. Practically no measurable response to the dosage which we decided to use was observed in about 25 per cent of the cases. Our patients were given 200 mg. as an initial dose instead of the recommended 300 mg. They were not given any more for forty-eight hours or until we knew the reaction. Often only one dose appeared sufficient while in others repeated doses were needed.

The response to the small doses was satisfactory in about 75 per cent of the cases while in about 25 per cent there did not appear to be a very good response.

We reduced the incidence of thrombophlebitis in postoperative cases in the controlled series at about the same ratio, that is about 75 per cent on the surgical series using the drug as compared to the incidence found on the series not using it.

The next will summarize the hemorrhagic complications we have observed in 903 patients who received Dicumarol prophylactically. Minor bleeding occurred in 26 patients. A few of these occurred in patients who had no response to the drug. I believe this indicates that our present laboratory tests are not sensitive enough.

Major bleeding occurred in 4 patients and 17 instances of phlebitis developed during the treatment. The 4 patients required femoral vein interruption. Twelve individuals in this group had infarcts to the lungs.

It is important to point out that none of the patients receiving Dicumarol as a prophylactic measure died of pulmonary embolism.

There were, however, two deaths from delayed hemorrhage that we believe were attributable to Dicumarol. Minor bleeding from Dicumarol in the small doses we used was no great surprise, but serious bleeding in four instances was unexpected and the two hemorrhagic deaths were due to a defect in the routine use of the drug, particularly in patients with hypertension and atherosclerosis.

I believe it is fair to say that if we knew enough about a Dicumarol properly we could have avoided the complications of hemorrhage as well as the instances of thrombophlebitis that occurred during its use.

One year ago before this Association I made the true statement that still applies
- - - - - valuable but the ones that we have at our disposal now are very dangerous
- - - - - to us too

taken at
on all the

with a twenty five foot cloth tape measure. This was done in order to magnify the total measurement so that slight errors in the rapid measurements required would not vitiate the result.

To perform the test the patient lies in a supine position with the limb elevated to about 45 degrees supported either by an assistant or a leg rest. After five minutes a point is selected and marked on the lateral aspect of the limb two inches above the distal tip of the external malleolus. The end of the tape is secured to this point by means of a strip of adhesive tape. The limb is then wrapped with twenty consecutive paralleled turns of the tape and terminated at a point directly in line with the initial point. The terminal point is marked and a direct reading made from the tape in feet and inches. This will result in the entire lower limb being almost enclosed by the tape (Fig 1 A). It is important in wrapping that (1) the tape rest against the skin and

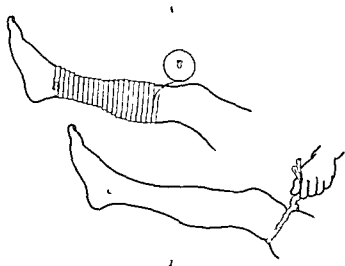


Fig 1—A The initial measurement is taken with the patient in recumbent position and the leg elevated at 45 degrees. Initial point is on lateral aspect two inches above the distal tip of the lateral malleolus. Twenty turns of the tape are taken. B With patient and limb in same position the tape is removed and a tourniquet applied to occlude the superficial venous system.

not be pulled up with any tension and (2) the successive turns lie parallel to one another and do not overlap. Where the contour changes suddenly as in the calf region no effort should be made to fit the entire width of the tape to the contour of the leg as this will result in spiraling. Parallelism can be achieved by resting the uppermost portion of the tape on the skin and allowing the lower portion to jut out.

The tape is removed and with the leg elevated a tourniquet applied above the knee (or if necessary to exclude the lesser saphenous vein just below the knee) with sufficient force to occlude the superficial venous system at this point (Fig 1 B). The patient is directed to stand with the tourniquet in place and the measurement is taken immediately (Fig 2 A). Before going from lying to the standing position the patient should be cautioned to stand

VENOUS AND LYMPHATIC STASIS IN THE LOWER EXTREMITIES

I A TEST FOR INCOMPETENCE IN THE PERFORATING VEINS

II A SIMPLE METHOD OF ADEQUATE CONTROL

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PERSISTENT venous stasis and chronic lymphedema in the lower extremity are always at least potentially dangerous. The increased protein rich extracellular fluid induces the development of fibrosis and provides a favorable environment for the establishment of infection. Pigmentation of the skin and induration of the subcutaneous tissues usually develop in time often complicated by a chronic cellulitis, a persistent dermatitis or acute inflammatory episodes of localized phlebitis or streptococcic infection. Eventually an ulcer appears either spontaneously or after a minor trauma and tends to persist on account of the impaired nutrition of the skin. This is the frequent late effect of venous stasis and lymphedema whatever its original cause. When obvious varicosities can be seen or when the engorged venous channels can be felt tests for incompetence of the communicating veins are available. With compression of the main saphenous channels the rapid filling of the emptied veins below the tourniquet on standing (Trendelenburg test) or the emptying of the full veins on walking (Ochsner Mahorner test) are simple and adequate. But when induration of the skin and subcutaneous tissues has occurred the veins can often neither be seen nor felt and these clinical tests become inadequate. Under these conditions a relatively rough comparative measurement of volumetric changes in the leg with change in position has proved useful to us in determining incompetency of the perforating veins.

A CLINICAL TEST FOR VENOUS STASIS WITH INCOMPETENT PERFORATORS IN THE LOWER LEG

The basis for taking the measurements rests on the hypothesis that a sudden change from an elevated to a dependent position would be expected to result immediately in an abnormal increase in the total limb volume if there were marked valvular incompetence in the veins. Many elaborate devices were considered for accurately measuring this volume change but all were rejected in that they failed to meet the two requirements which we considered paramount, namely (1) that the measurements be taken readily with the patient in the recumbent and the standing positions and (2) that an apparatus be used which would not be too complicated for clinical application. Dr. W. O. Irena suggested using the average circumference of the lower leg a method which he had seen employed on experimental animals in Dr. Joseph Aub's laboratory. Rather than taking multiple individual circumferential measurements of the limb as done by Dr. Aub we decided on a continuous wrapping

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selecting the proper form of treatment when the indurated edematous condition of the limb masked all attempts to demonstrate incompetency of valves or even the presence of superficial varices by any of the proved conventional clinical methods. Also it served as a useful guide as to the effectiveness of the surgical procedures performed to improve the venous stasis. The following two cases will illustrate that point.

CASE REPORTS

L. S. (No 202765) a 61 year old white unmarried woman noted edema of right and left lower legs with subsequent ulcerations over the medial aspect of the right ankle. For eight years previous to being seen by us she had had numerous ligation injections and skin grafts. The right lower leg improved and the ulcers healed but the left continued to ulcerate and swell. Examination of the left lower leg showed an edematous indurated pigmented extremity with two areas of ulceration just above the medial malleolus and in the midcalf region. Ithelograms of dye injected into the superficial varices of the left ankle showed the dye to pass rapidly through unusually large perforating vein into the deep circulation in the midcalf.

Measurements of the left lower leg on Nov. 9, 1947 following two days absolute bed rest were: Elevated 18.4" standing with tourniquet 20.0" standing without tourniquet 20.6" elevated 18.11"

On Nov. 1, 1947, ligation of the left superficial femoral vein was performed.

On Jan. 1, 1948 the symptoms were somewhat less but there was evidence of marked venous congestion in the left lower leg. Measurements were: Elevated 20.10" standing with tourniquet 21.10" standing without tourniquet 21.9 1/2" elevated 21.0"

When seen on April 16, 1948 the patient was fully ambulatory. Four months had elapsed since dissection and ligation of all perforators on the lateral aspect of the left lower leg. Symptoms were considerably improved with marked diminution of edema and induration. Measurements at this time were: Elevated 18.9" standing with tourniquet 19.6" standing without tourniquet, 19.8" elevated 18.11"

The last set of measurements revealed considerable improvement but it was felt that considerable incompetency still existed. Shortly thereafter dissection and ligation of all perforators on the medial aspect of the left lower leg were performed. Unfortunately we do not have a measurement following this procedure.

J. T. (No 19876) a 49 year old married housewife noted bilateral varicosities following her first pregnancy twenty eight years previously with an increase in them following the second pregnancy. She was asymptomatic with no evidence of phlebitis. Ten years before varicosities had been treated by injection with improvement. In October 1947 however she noted appearance of ulcerations on the anterior aspect of the left lower leg.

Examination showed markedly enlarged varicose veins in the greater saphenous system with some demonstrable incompetence of the perforating vein of the left lower leg. Multiple small superficial ulcerations were present over the anterior aspect of the left lower leg. The right leg had no large varicosities and no incompetence of the perforators could be demonstrated clinically.

Measurements on Nov. 14, 1947 were: Elevated right 19' 6 1/2" left 20.8" standing with tourniquet right 19.8" left 21.9 1/2" standing without tourniquet right 19.8" left 21.8" elevated right 19.6" left 21.1"

On Nov. 14, 1947 a high ligation and division of the left greater saphenous vein just distal to the junction with the femoral were performed with ligation and division of all entering branches.

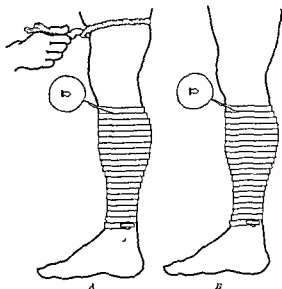
On Nov. 1, 1948 a cecum thrombosis of left greater saphenous system was noted from midcalf to the groin.

On Nov. 4, 1947 the thrombosis was still present. Measurements on the left were: Elevated 20.1" standing with tourniquet 20.6" standing without tourniquet, 20.7" elevated 19.11"

with the heels about twelve inches apart, and to bear his weight equally on both feet

Following the second measurement the tourniquet and tape are removed and for an interval of five minutes the patient is directed to stand as quietly as possible. After this interval a third measurement is taken without the tourniquet in place (Fig 2 B). (It is convenient to have the patient on a small platform stool about twelve inches in height, and to have the operator sit on the floor straddling the stool.)

The fourth measurement is taken the same as the first after the patient has again reclined on the table and elevated the limb for five minutes.



Patent
B Third
toed still

When normal lower legs—that is, those with no evidence of arterial or venous pathology—were measured by the technique described the maximum increase in measurement was found to be six inches. Very often the changes were only slight and amounted to three inches or less. Any increase over six inches, and particularly in the second measurement (standing with the tourniquet on) was regarded as indicative of venous stasis. Patients with obvious varicose veins, but with no incompetency of the perforating veins showed by clinical tests no abnormal increase in volume until removal of the tourniquet.

However, the most marked measurement changes were noted in patients with incompetency of the perforating veins. The greatest increase was always on the second measurement and in some cases was as great as twenty inches. We ascribed considerable importance to this fact and found it very useful in

vent further increase in volume. In the first category are compression bandages, made of cotton alone or reinforced with elastic strands or made entirely of rubber and elastic stockings. The defect in all of these is that where bony and tendinous elevations occur in the lower leg and around the ankle effective uniform pressure cannot be obtained in the depressions between the prominences. Recognizing this drawback, perhaps the most effective physical method of overcoming the venous stasis in the lower part of the lower leg previously has been the incorporation of some type of sponge rubber under the elastic bandage in the lower leg as suggested by McPheters. However even this method does not give a uniform pressure in all areas. In the second category the outstanding example is the Unna gelatin paste boot. When accurately applied it holds the volume of the leg to that of the time of application but it does not produce any elastic compression of the enlarged veins nor does it compensate for any decrease in size.

In order to overcome the defects present in the previous forms of compression it seemed to us that the simplest method to get a uniform pressure throughout the lower leg was by the use of a compression dressing containing an inflatable bladder with a nonelastic sheath. Any desired pressure on the leg can then be obtained by adjustment of the pneumatic pressure. Six years ago we were confronted with the problem of a serious venous stasis in the postphlebotic extremity of W. I. The usual methods of physical restraint and operative treatment had failed to prevent the recurrence of venous stasis with ulceration in the vicinity of and below the malleoli. The great saphenous vein had been ligated above all branches. It had been stripped out to a point below the knee and had then been removed from the knee to the ankle. Flaps had been turned back to beyond the edge of the tibia nearly to the midline posteriorly and all perforating vessels ligated. The lesser saphenous vein and perforators associated with it had also been divided. These operative procedures produced a healing of the ulcer in the lower leg but the patient developed large tense veins connected with the numerous perforators below both malleoli in the posterior part of the foot. An ulcer was forming below the external malleolus and pre-ulceration was present below the internal malleolus. Treatment was begun with air pressure applied in a football bladder about the ankle and lower leg under a canvas legging apparatus constructed by the patient who was an experienced engineer. Within one week the ulcers below each malleolus were completely closed and the purplish discoloration and the burning sensation present in these areas had disappeared. This had occurred during a period of intense activity on the part of the patient. A pneumatic legging has been used by this patient continuously since then. At one time during the war he had to spend one week in Washington. The football bladder developed a worn area and he could not get a replacement for it. Within three days the ulceration below the external malleolus had recurred. The football bladder was repaired and treatment resumed. Immediately the discomfort in the leg disappeared the ulcer began to heal and within one week was completely healed. Following the success of this method

The decrease in the postural measurement difference we felt was associated with the ascending thrombosis or lodging the perforating veins rather than a *permanent improvement* in the degree of incompetence in the perforator. That this assumption was correct is shown by the last measurements on May 20 1949. Elevated, 21.0 standing with tourniquet, 21.11 standing without tourniquet 21.10, elevated, 20.11.

These cases illustrate the manner in which measurements of the postural effect on the volume of the leg are useful. The latter can assist in the determination of venous stasis due to incompetent perforators even in the absence of visible or palpable varicosities and also in following the effect of various therapeutic measures. We have demonstrated marked incompetence of the communicating veins in many cases of the postphlebotic state when this fact could not be shown by the usual clinical tests (due probably to the fibrosis and induration present).

Two conditions may prevent the marked difference in postural change that we have come to associate with incompetent perforators namely (1) an acute inflammatory reaction in which probably the acute swelling already present prevents or masks the postural increase in volume and (2) an acute thrombosis in the subcutaneous veins in which in addition to the above cause many of the perforators may actually be temporarily obstructed by a blood clot.

TREATMENT

When the venous stasis is due only to incompetence of the valves in the greater and lesser saphenous veins themselves the high division of the main channels will suffice to correct this. But when there is a major degree of incompetence in the communicating veins then the correction of the venous stasis becomes much more difficult though usually even more imperative. Unfortunately there are a great many communicating veins throughout the lower leg and below the ankle. When they have become incompetent usually this has been due to an inflammatory process either following a deep thrombophlebitis or as a complication of long standing varicosity with superimposed infection. Then involvement is diffuse even though a few of them have become greatly enlarged. If the latter are divided others will dilate and the venous stasis will recur. It is for this reason that the surgical treatment of venous stasis associated with incompetent perforators has become so radical. When the greater and lesser saphenous veins have been removed from the knee to the ankle and the flaps undermined extensively to divide the perforators—a rather extensive surgical procedure—even then communicating veins below the ankle on each side may develop into large incompetent channels and re-establish the venous stasis.

Physical measures for the control of the venous stasis are numerous and sufficient in many instances. However all of these previously in common use have one serious defect namely that they do not effectively overcome the venous stasis in the lower part of the leg and below the ankle. In general these measures use one of two principles: (a) the compression of the dilated veins by a circular bandage or stocking usually incorporating the principle of elastic tension or (b) the application of an inelastic dressing which will pre-

Cape Cod duck casing closed with a zipper and containing a butterfly shaped rubber bladder which is inflated through a tube and valve at the top of the legging (Figs 3 and 4). The hand pump used for inflation has a regulator which automatically controls the air pressure left in the bladder. It has been found empirically that an initial pressure within the bladder of about 35 mm Hg appears to be optimal in most cases*. One other significant fact has

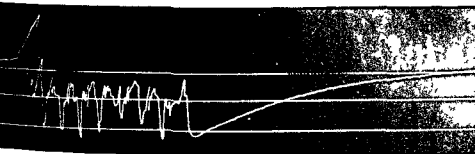


Fig 5

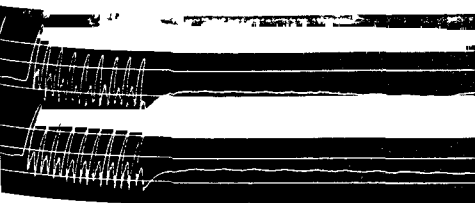


Fig 6

been found by recording the pressure within the balloon during walking. With the contraction of the gastrocnemius group of muscles the pressure within the balloon rises above the initial pressure and with relaxation the pressure falls below the initial pressure in a cyclical manner (Fig 5). This is

It is interesting to note that approximately the same pressure was found of benefit when applied to full thickness grafts while higher pressures were injurious. Ferris Smith, A Practical Management of Skin Grafts. Surg. Gynec. & Obst. 45: 6, 1956.

of overcoming venous stasis where all the commonly used methods had failed the same type of homemade apparatus was used on twelve other patients in the ensuing five years. In each instance the venous stasis was kept under adequate control and the individual's activity was not interrupted.



Fig. 3—Aero pulse legging consisting of an outer duck casing containing a butterfly shaped balloon in an inner pocket.



Fig. 4—Aero pulse legging applied. The balloon is inflated to the determined pressure (usually 35 mm Hg) automatically controlled by the regulator on the interior.

In the last year upon my request this first patient a trained mechanical engineer has designed a legging which effectively applies this principle of uniform air pressure throughout the whole lower leg. It consists of an outer

This appliance can be obtained under the name Aero Pulse Legging from the Surgical Research Corporation 1310 Crittenden Road Rochester N. Y.



Fig. 8

Fig. 9

Fig. 10



Fig. 11

Fig. 12

Figs. 8, 9, 10, and 11.—J. Bilateral postphlebotic, late. On the right ulceration is controlled by conventional elastic compression. On the left ulceration cannot be prevented thus. Fig. 12 condition just before applying Aero-pulse legging. Fig. 8 after using the legging one month. Fig. 9 after using the legging one month. Fig. 10 after using the legging one month.

true whether the perforators are competent or not (Fig. 6). The result is that the subcutaneous tissues of the leg are exposed to a pulsating pressure during activity in a similar manner to that applied by muscular contraction to the deep veins. In other words in effect a deep fascial has been placed outside of the skin and the subcutaneous veins and lymphatic spaces are compressed rhythmically on walking. It is our belief that this pulsating pressure powered by the muscle contractions in the upper part of the lower leg and exerted uniformly (in spite of its irregular contour) on the skin and subcutaneous tissues throughout the whole lower leg is an important factor in driving out the excess of extracellular fluid. If this is so then exercise by the patient wearing such a legging is beneficial rather than detrimental. The latter conclusion would seem to be borne out by the following case.

CASE REPORTS

C. J., a 16 year old boy, sustained an epiphyseal separation of the right femur in 1945. He subsequently developed phlebitis and persistent swelling of both legs. The postphlebitic condition in the right leg has been kept under fair control by elastic restraint though he still has continuous swelling in this lower leg with extensive pigmentation. In the left lower leg an ulcer formed which was not amenable to treatment by elastic restraint. The only way healing could be induced was by putting the patient in bed with the leg elevated. In three months time with complete bed rest and elevation of the leg, the ulcer was reduced to about one third of its original size. The Aero-Pulse legging was applied on Dec. 3, 1948 after the ulcer had returned to its previous size. In six weeks' time with continuous activity the ulcer had healed to the same extent that it had previously done in three months of elevation and bed rest (Figs. 7, 8, 9 and 10). It continued to heal until there was only a small area about 2 mm. in diameter over the center of the ulcer. At that time the zipper of the legging broke and the patient continued activity without effective pressure until his next appointment in ten days. The ulcer began to enlarge within three days and it measured 17 by 11 cm. in diameter when he was next seen (Fig. 11). It has now rapidly healed again with the reapplication of effective pneumatic pressure.

This case illustrates two facts: (1) the greater effectiveness of the legging in healing the ulcer with continued activity as compared to the healing of the ulcer with immobilization in bed and elevation of the extremity and (2) the rapid recurrence of ulceration when the effective pressure is removed.

Fifty-two patients with severe venous stasis and chronic lymphedema have been treated with the pneumatic legging. In general it can be stated that any lymphedema which can be made to disappear by elevation of the extremity will be effectively controlled. Ulceration due to persistent venous stasis and not associated with an acute phlebitis or acute cellulitis will begin to heal promptly and the rate of healing appears to be at least as fast with the patient ambulatory and active as can be obtained by elevation of the extremity in bed. The amount of scar tissue in the ulcer base and fibrosis in the surrounding area will undoubtedly be a limiting factor in the healing of some of these ulcers but we have been surprised by the strikingly increased vascularity of the ulcer base and the capacity of such long standing ulcers to heal. The induration of the subcutaneous tissues gradually diminishes even the dense pigmentation of the skin often becomes much lighter and recurrent attacks of cellulitis and flare-ups of subcutaneous phlebitis seem to be prevented or to occur less frequently. Twenty-six of the patients have required

When the ulcers appear below the malleoli we have found that 35 mm Hg of pressure in the balloon may not be optimal. This is probably due to the fact that the elastic tension of the rubber in the prolongation of the balloon below the malleoli absorbs some of the effective pressure to be exerted on the skin in this area. We have found that more rapid healing of such ulcers can be obtained by a pressure of 50 mm Hg. However if the pressure in the balloon is increased to this level the patient may notice some discomfort. Under these circumstances, therefore, a second small bladder is placed below



Fig. 1.—H. K. Post-traumatic ulcer. A, eight months after injury. Healing of the ulcer has been prevented by venous stasis (varicose veins with incompetent perforators) in spite of conventional elastic dressings. B, two months after using the Aero-pulse legging. Laceration healed in one month without interruption of the patient's work.

the malleoli and filled with air at a pressure of 50 mm Hg while the pressure in the main bladder is kept at 35 mm Hg (Fig. 13). This auxiliary bladder at a slightly higher pressure below the malleoli has been used in three cases with rapid healing of the ulcers in this situation in each case (Fig. 14).

A chronic dermatitis is a frequent complication of venous stasis and is sometimes the outstanding clinical feature. The dermatitis often will not yield to treatment until the venous stasis is overcome. Certain special precautions are necessary, however, with the use of the legging in these cases. The increase in moisture and temperature of the skin favors the persistence or even the exacerbation of the dermatitis. We have found this unfavorable

treatment for postphlebotic sequelae (lymphedema induration, ulcer formation recurrent attacks of cellulitis or of subcutaneous phlebitis, and stasis dermatitis) Eighteen of the cases have been those of long standing varicosities with incompetent communicating veins (perforators), frequently with trauma as the factor precipitating a resistant infection and ulceration. In three cases of severe acute iliofemoral thrombophlebitis the Aero pulse legging has been applied as soon as the patient was ambulated in an effort to minimize the late postphlebotic effects, in three cases the chronic lymphedema was from other causes not apparently associated with varicosity or the postphlebotic state. The following cases illustrate the usefulness of this method of treatment.

C M a 51 year old steel worker, was first seen in 1944. He had had varicose veins in the left leg since an injury seven years previously. In 1942 he developed an open ulcer above the internal malleolus following repeated trauma to this area by the clutch pedal of the machine operated.

several sclerosing injections of the varicosities in the lower leg produced temporary improvement which was completely lost on return to work. For two years from 1945 to 1947, he was not seen by us and at the end of this time his condition was unimproved. The great saphenous vein in the lower leg was removed with exposure and division of incompetent perforators on the medial and lateral sides of the leg. Following this he again showed improvement for a few weeks but recurrent attacks of superficial phlebitis and cellulitis persistently occurred, associated with ulceration in the involved area. The inflammatory attacks subsided on bed rest with antibiotics but they would recur with activity in spite of the usual type of compression dressings. In November, 1948 the flare-ups of inflammation occurred whenever the patient resumed any activity and the induration of the subcutaneous tissues was unaltered or possibly progressive. The Aero pulse legging was applied and the patient was made ambulatory. In one month all ulcers had healed, the induration of the subcutaneous tissues was beginning to soften up and the patient had had no inflammatory attacks. By the middle of January 1949 the patient returned to his regular work at which he has continued to the present. Although we know by measurement that there is serious incompetence of remaining communicating veins* the venous stasis is adequately controlled by the legging. Undoubtedly this patient could have been saved four years of unemployment by the use of this method of treatment originally.

II F a 44 year old truck driver had a rather unremarkable medical history. He had large varicose veins on the right leg. In February 1948 he had an abrasion over the anterior surface of the right lower leg followed by ulceration and infection and associated with swelling of the right lower leg. When first seen this had persisted for six months without improvement. He continued at work. Examination showed a major degree of incompetent

In five weeks the ulcers had completely healed and the induration about the ulcerated area had greatly diminished. This patient had a very similar condition to that of the previous one. He had gone for eight months without improvement after his injury. The ulceration and infection had reached the point where he could not continue at his work. However they were rapidly and completely cleared up by the treatment without interfering with his activity.

When first seen on July 30, 1947 the difference between the elevated and standing with tourniquet in place was 1 1/2 inches. On May 13, 1949 the difference was 1 1/4 inches.

dermatitis when the element of stasis is overcome. Exceptionally, however, the elements of infection, bacterial or fungus, have to be brought under control by energetic treatment in bed before the legging is applied. Such instances of extremely resistant infections are we believe quite rare. One other complication which has arisen infrequently in conjunction with the use of the legging is a diffuse papillary eruption of the skin particularly apt to occur during warm weather. In two instances we believe this condition was due to a sensitivity of the individual to some ingredient of the rubber. When this occurs it can be prevented by an insulating layer of inert plastic or cellophane between the bladder and the skin. Also in very warm weather some patients develop an excess of perspiration which may irritate the skin. This can usually be prevented by wearing an understocking with a layer of Cellu cotton wrapped about it under the legging.

When venous stasis is controlled by the use of the legging this has to be continued indefinitely whenever the patient is up and about. However we have found that after the control of the ulceration and induration the patient can be without the pneumatic pressure for a fraction of the day. This will undoubtedly vary from one case to another but we would estimate that this interval would usually be between 10 and 25 per cent of his activity. Thus most individuals could probably be without such support for one to three hours in the evening, for example. This is ordinarily not too important to the male patients but is much appreciated by the women. Of course support can be dispensed with whenever the leg can be elevated.

Until recently, care has been taken to exclude from such treatment any one showing signs of a major arteriosclerotic element in the condition of the lower legs. This was done because we feared a deleterious effect of the pressure of 35 mm Hg. on the skin under these conditions. A recent experience, however, leads us to believe that if there is an element of venous stasis in the lower leg its control in this manner may be beneficial in spite of the arteriosclerotic component.

Case 8: a 67-year-old janitor on Feb. 12, 1949, dropped an oil can on his left shin skinning the surface in several places. The abrasion became infected and developed into an intractable ulcer which failed to heal and he has not been able to work since injury. Before the accident he had only noted occasional cramps in both legs at night and a feeling of coldness in the feet and he probably had had mild dependent ankle edema but he had not observed any ulceration.

On examination he had an ulcer 2 by 3 cm. on the anterior surface of the left lower leg with smaller ulcers in the region of the left internal and external malleoli. The skin in the whole lower half of both lower legs was pigmented, crusty and scaling with areas of atrophy and a small open ulcerated spot on the posterior surface of each lower leg. There was slight bilateral ankle edema. There was no pulsation felt in either leg below the femoral artery. On elevation ischemic pallor developed in both feet and on resuming the horizontal position there was a slow return of capillary circulation on both sides. There were some moderate varicosities in the left leg and there was a distinct purplish cast to the skin in the left lower leg particularly about the ulcers.

It was felt that he had marked arteriosclerotic changes in both lower legs with definite skin changes from this cause. In addition to this he had post-traumatic ulcers on the left leg and also a component of venous stasis. On the possibility that the latter might be the de-

effect on the dermatitis can usually be overcome by two measures (1) the active treatment of any element of fungus infection in the skin, usually half strength Desenex ointment is effective for this purpose (2) the absorption of any moisture from the skin, a cotton understocking is worn under the legging



Fig. 13—Acute leg ulcer with an additional ankle blister for ulcers below the malleoli. The pressure in the auxiliary small blister is maintained at 50 mm Hg while that in the main blister remains at 25 mm Hg.



Fig. 14—Illustration of the type of ulcer in which the auxiliary blister is used. These ulcers were healed by this technique in less than one month.

and if necessary a layer of Cellu-cotton is wrapped around the leg, before the legging is applied.* These measures will usually suffice to control the

*An old Ace bandage loosely wrapped about the leg over the understocking before applying the legging has been used in place of the Cellu-cotton as an absorbent layer in some cases. It must not constrict the leg or the radiant force of the pneumatic pressure is lost.

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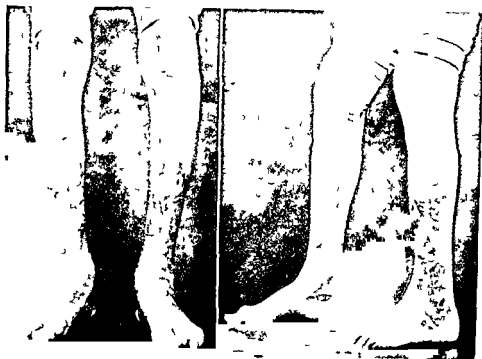


Fig 1—N. S. 1. Attrunmatt ulcer. Venous stasis is associated with marked arteriosclerotic skin change. Three months after injury there was no sign of repair.



Fig 10—N. S. Three weeks after using the Aero-pulse legging. The large ulcer on the anterior surface of the left lower leg is now less than one half its former size and the ulcers near the malleoli are completely covered with new epithelium.

terminal factor in the failure of the ulcers to heal an A. V. pulse blocking was applied to the left leg on April 22, 1949. Three weeks later the ulcers near the malleoli had both healed and the larger ulcer in the middle third of the anterior surface had decreased in area by at least one-half (Fig. 15 and 16). The ulcer went on to complete healing.

It can be definitely stated that in spite of a marked arteriosclerotic element the degree of pressure used to overcome the venous stasis has not been detrimental and it has seemed to be very beneficial in the healing of these ulcers. Probably an arteriosclerotic ulcer uncomplicated by any element of venous stasis would not be benefited by the use of the pneumatic pressure though even this assumption may be untrue.

CONCLUSIONS

1 Venous stasis in the lower extremities may be demonstrated clinically even when the superficial veins can be neither seen nor felt.

2 In the application of pneumatic pressure made to pulsate by muscular contraction lymphedema and venous stasis have been effectively controlled induration of the subcutaneous tissues has been reduced ulcers resistant to treatment by the usual compression dressings have been healed and recurrent attacks of cellulitis and phlebitis have been curbed.

3 The injurious effect of incompetent perforators can be controlled without operation.

4 Stasis dermatitis requires special precautions in this form of treatment.

5 A pressure of 7 mm. Hg. has been found optimal in most cases. When the ulcer is below the level of the malleoli 50 mm. Hg. in an auxiliary small bladder may be desirable.

DISCUSSION

DR. M. E. DEBAKEY.—Dr. Laikovich and Dr. Scott are to be commended for the development of this ingenious device for providing a controlled evenly distributed pressure dressing. It reminds me of a somewhat similar device which Dr. Beverly Douglas, Nashville developed about ten years ago.

The efficacy of pressure dressing in certain conditions has long been well recognized and the principle upon which this device is based is similar to that of the simple and commonly employed elastic bandage. As pointed out by Dr. Laikovich and Dr. Scott however it has the advantages of providing a controlled and more evenly distributed pressure. Whether or not in actual practice the advantages outweigh the greater simplicity of the elastic bandage remains to be determined by practical experience.

Of particular interest to those of us from the deep South is the discomfort associated with the wearing of such a device in the summer time and the consequent effects of increased perspiration and skin irritation. Indeed this is one of the objectionable features of the elastic bandages among patients who must wear the bandages for long periods during the hot summer season. It may be of interest to observe here that among patients who have had sympathectomy as part of the treatment because of a associated excessive vasospasm the objectionable features are greatly minimized probably due to the absence of sweating.

Of particular importance in considering pressure dressing or elastic supportive measures in the treatment of postphlebotic leg ulcers is the fact that while such therapy is effective in providing healing of the ulcer recurrences are common after it is discontinued. The difficulty in this problem is the maintenance of healing. It is for this reason that we, like others have attempted to use certain operative procedure including

sympathectomy and other measure directed toward improving the local circulation and correcting venous insufficiency. In this connection it may be of interest to present briefly the results of a recent analysis of our experience with 24 cases of this kind with follow-up studies of six months or longer. Conservative measures alone with primary emphasis on pressure dressings were used in 11 per cent and operative procedures including sympathectomy were employed in the remainder. In the former group definite improvement was obtained in about 44 per cent of the cases whereas in the latter such improvement was secured in about 57 per cent. This becomes even more significant when it is realized that the operative procedures were usually employed for the more severe cases while the conservative methods of therapy were most commonly applied to the milder cases.

THE WALKING VENOUS PRESSURE TEST AS A METHOD OF EVALUATION OF VARICOSE VEINS

EUGENE A. WHITE, M.D.* AND RICHARD WARREN, M.D.† WEST Roxbury, Mass.

THERE are two causes of venous stasis of the lower extremity which are the result of local venous disorders. They are incompetency of the superficial or saphenous system of veins due to varices and incompetency of the deep or femoropopliteal system of veins due to damage of its valves by phlebitis.^{1, 2} The identity of local factors responsible for symptoms in venous stasis namely heaviness and fatigue and those responsible for its complications namely edema pigmentation and ulceration of the skin have given rise to much speculation. Homans³ has mentioned the lymphatic stasis which occurs after phlebotomy alba dolens. Thompson⁴ drew attention to the role of infection particularly by fungi. Oschner⁵ has emphasized the damage caused by arteriofar spasm during the more acute phase of the thrombophlebitic process. Hallock⁶ seems to have ruled out successfully local anoxia of the venous blood. All however have known that whether or not it is the direct cause of the complications as Dolbet⁷ thought and Mahorne⁸ has more recently emphasized in abnormal venous pressure exists in venous stasis of the lower extremity.

The exact definition of the derangement of venous pressure in clinical venous stasis was appreciated by Freundlenburg⁹ and by Perthes¹⁰ and was measured quantitatively by Boecker¹¹ and by Scro¹². Adams¹³ and Veil and Hussey¹⁴ have also thrown important light on the pressure defects in these conditions.

If pressures are measured in the superficial veins there is no difference in venous pressures between normal extremities and those suffering from venous stasis when individuals are in the recumbent position or when they are up right and at rest. In the former situation the pressure is equal to the normal venous pressure of the individual in the latter to that pressure plus an increment represented by the hydrostatic pressure of the column of blood between the right auricle and the point tested. The abnormality in the extremity with venous stasis appears only on walking when the pressure in the superficial veins due to valvular incompetency falls very little or not at all or even shows a slight rise. In the normal extremity a rapid fall takes place to a level represented by a point somewhere between the individual's hip and knee.

Veil and Hussey¹⁴ alone have measured pressures in the deep system. They have made the important observation that the pressure fluctuates during the step but that the mean pressure in the normal extremity does not rise or fall during exercise. In the extremity with deep venous obstruction however there is a progressive rise of pressure in the popliteal vein during exercise.

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In a previous communication we have described a test,¹¹ essentially a Perthes test which can be read in numerical values, in which these principles as they relate to the superficial veins are applied to the evaluation of clinical cases.

In that communication the technique of the walking venous pressure test was demonstrated and average pressure values for three types of extremity, normal varicose, and postphlebotic were presented. If the zero point for measurement was taken as the resting erect venous pressure (REVP) the mean value for walking erect venous pressure (WEVP) was found to be -51.7 cm in normal -26.6 cm in varicose, and -1.8 cm in postphlebotic extremities. The mean values for walking with saphenous occlusion (WEVPSO) were -45.2 cm in normal -57.2 cm in varicose, and 0.7 cm in postphlebotic extremities. It was demonstrated in a group of postphlebotic extremities that femoral vein ligation did not consistently improve venous function as demonstrated by the test. There was also little evidence that obliteration of the superficial veins in these extremities would tend to do so. It is the purpose of the present report to set forth further observations on extremities with venous stasis with particular reference to those suffering from pure varices of the saphenous system without involvement of the deep or femoropopliteal system.

Over a two year period, walking venous pressure tests were performed on 119 extremities suffering from venous stasis. Of these, 21 were postphlebotic and 98 were purely varicose in origin. During the study we have attempted to answer several controversial questions which frequently appear in clinical discussions over such patients.

Diagnosis of Pure Saphenous Varices—Although the diagnosis of pure varices of the saphenous system can easily be made when there are no complications such as edema, pigmentation, or ulceration, the matter is not so simple when these signs are present. Several methods have been used in the past. Testing by the method of Trendelenburg in which the speed of filling of the veins below a thigh tourniquet is noted when the limb is changed from the elevated to the dependent position and by the method of Perthes in which the speed of emptying of veins below a venous tourniquet in the thigh is noted when the patient walks is often difficult to read in the presence of skin changes or edema. Fig. 1 presents the data on 21 postphlebotic extremities which were tested by the walking venous pressure method. In 11 of these 21 extremities the generally accepted Perthes and Trendelenburg tests were not clear and the diagnosis was settled by the pressure readings.

A history of past phlebitis is of help in making a presumptive diagnosis. It is not, however, completely reliable. This we have noted to be particularly true in patients who develop phlebitis following fractured femurs in which the apparatus which immobilizes the fracture tends to conceal the acute episode of phlebitis and the subsequent swelling is attributed to "posttraumatic" edema and not to thrombosis. This occurred in 2 extremities of our group.

The appearance of the limb is often taken as a means of making the diagnosis. We have found this method totally unreliable. Fig. 2 shows the

In a previous communication we have described a test,¹ essentially a Perthes test which can be read in numerical values in which these principles as they relate to the superficial veins are applied to the evaluation of clinical cases.

In that communication the technique of the walking venous pressure test was demonstrated and average pressure values for three types of extremity: normal, varicose, and postphlebitic, were presented. If the zero point for measurement was taken as the resting, erect venous pressure (REVP), the mean value for walking erect venous pressure (WEVP) was found to be -51.7 cm in normal, -26.6 cm in varicose, and -1.8 cm in postphlebitic extremities. The mean values for walking with saphenous occlusion (WVPO) were -45.2 cm in normal, -57.2 cm in varicose, and 0.7 cm in postphlebitic extremities. It was demonstrated in a group of postphlebitic extremities that femoral vein ligation did not consistently improve venous function as demonstrated by the test. There was also little evidence that obliteration of the superficial veins in these extremities would tend to do so. It is the purpose of the present report to set forth further observations on extremities with venous stasis with particular reference to those suffering from pure varices of the saphenous system without involvement of the deep or femoropopliteal system.

Over a two year period walking venous pressure tests were performed on 119 extremities suffering from venous stasis. Of these, 21 were postphlebitic and 98 were purely varicose in origin. During the study we have attempted to answer several controversial questions which frequently appear in clinical discussions over such patients.

Diagnosis of Pure Saphenous Varices—Although the diagnosis of pure varices of the saphenous system can easily be made when there are no complications such as edema, pigmentation or ulceration the matter is not so simple when these signs are present. Several methods have been used in the past. Testing by the method of Trendelenburg in which the speed of filling of the veins below a thigh tourniquet is noted when the limb is changed from the elevated to the dependent position, and by the method of Perthes in which the speed of emptying of veins below a venous tourniquet in the thigh is noted when the patient walks is often difficult to read in the presence of skin changes or edema. Fig. 1 presents the data on 21 postphlebitic extremities which were tested by the walking venous pressure method. In 11 of these 21 extremities the generally accepted Perthes and Trendelenburg tests were not clear and the diagnosis was settled by the pressure readings.

A history of past phlebitis is of help in making a presumptive diagnosis. It is not however completely reliable. Thus we have noted to be particularly true in patients who develop phlebitis following fractured femurs in which the apparatus which immobilizes the fracture tends to conceal the acute episode of phlebitis and the subsequent swelling is attributed to "posttraumatic" edema and not to thrombosis. This occurred in 2 extremities of our group.

The appearance of the limb is often taken as a means of making the diagnosis. We have found this method totally unreliable. Fig. 2 shows the

walking venous pressure tests on 7 extremities which had edema, pigmentation and ulceration. These extremities would have been diagnosed by many on their appearance alone as being postphlebotic. The Perthes and Trendelenburg tests without benefit of direct venous pressures demonstrated competency of the deep system in 3 of these 7. The walking venous pressure method however was necessary to make the diagnosis in the other 4.

Venography has been helpful but is not entirely reliable. Fig. 3 shows venograms of three types, one which demonstrates no filling of the femoral vein in the thigh, one which demonstrates poor filling, and one which demonstrates normal filling. The first and third patients had postphlebotic damage of the deep system as is evidenced by gross examination of the cross sections of the excised superficial femoral veins; the second extremity was purely varicose. All of the 15 venograms which we have performed in our group of 21 postphlebotic extremities have shown either poor filling or no filling of the femoral vein. Even though the venograms have coordinated well with venous pressure findings in this group we have never felt confident that no filling or filling without visualization of valves may not be due to a temporary whim of a normal venous circulation as to which system, the superficial or deep, is going to accept all or part of the contrast medium. The walking venous pressure response is a test performed under functional conditions.

Inspection of the femoral vein directly at the operating table is also not reliable. In 2 patients who received femoral vein ligation for postphlebotic stasis the external appearance and palpable consistency of the vein were normal. This was so much so that at the operating table we immediately feared that our preoperative walking venous pressure tests had misled us. Fig. 4 however shows the appearance these 2 veins presented when cut across and leaves no doubt as to previous thrombosis with later recanalization. The duration of time which had elapsed since the thrombotic episode cannot be used to explain the lack of expected reaction in the venous wall in either of these patients. One had phlebitis 25 years, the other 3 years prior to operation. Conversely we have seen (Fig. 5) a patient with pure varicose veins who had so much secondary infection in the calf with chronic lymphangitis that the scarring about the femoral vein in the groin made it adherent to the femoral artery in a manner usually considered to be characteristic of the postphlebotic condition. Yet this patient's walking venous pressures were characteristic of pure saphenous varices.

We have considered therefore that the walking venous pressure test has given us a better method than any other of making sure that we are dealing with pure incompetency of the saphenous system.

*Diagnosis of Which Elements of the Saphenous System Are Involved—*Four of the extremities with pure saphenous incompetency had varices which were maximal on the inner side of the leg in the area customarily thought to be the province of the long saphenous vein but which were demonstrated by test to be due entirely to incompetency of the short saphenous vein (Fig. 6). It is true that in all these patients short saphenous vein incompetency had

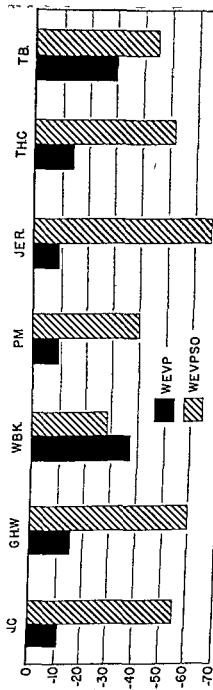
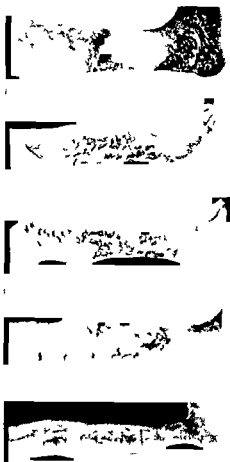


Fig. 2—Walking venous pressure (JC) is on exten- with pure aphenous vari- causing skin changes of derma surge (JC) of the
 po tobi b the stat. All (WBK) of the extremity show the type of skin changes that are additional
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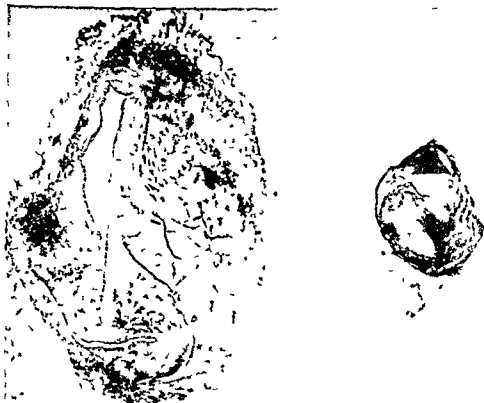


Fig. 4.—Two recanalized superficial femoral veins which were normal to external examination at the operating table



Fig. 5.—The normal femoral vein excised from a patient in the face of typical varicose pres ure re pon es be au e of sutrouning thick ring



Fig 4—Two recanalized superficial femoral veins which were normal to external examination at the operating table



Fig 5—The normal femoral vein excised from a patient in the face of typical varicose pressure is rescanable because of surrounding thickening

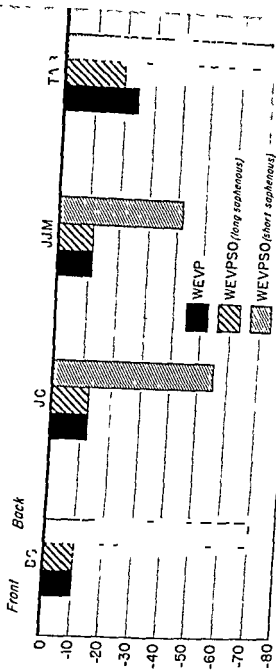


Fig. 6.—Extralittoral and littoral species in the walking zone of the calf, categorized by the number of species. The percentage of species in the walking zone of the calf was controlled by the number of species in the walking zone of the calf. The percentage of species in the walking zone of the calf was controlled by the number of species in the walking zone of the calf.

been suggested by the Trendelenburg and Perthes tests prior to the walking venous pressure determinations. The direct measurements given however serve to establish this as a definite fact and to caution the unwary who might overlook incompetency of the short saphenous vein when the varices are on the medial face of the calf. There were 12 extremities which showed recurrence of symptoms after previous surgery here or elsewhere and received study by the walking venous pressure test. Five of them had definite incompetency of the short saphenous vein which had been presumably overlooked in the original preoperative examination.

Incompetent veins communicating between the superficial and deep systems other than internal and external saphenous veins have been occasionally observed in the thigh. The type of extremity in which they occasionally become demonstrable is the one which has undergone long saphenous vein ligation high in the femoral triangle and which at a later date exhibits no fall in the walking venous pressure when digital occlusion is applied in this region but does show a fall in pressure when it is applied at the femoral condyle (Fig 7). The incompetent communicator here is obviously in the thigh.

We have not demonstrated incompetent communicating veins in the calf in the absence of incompetency of the deep system. Such incompetency would obviously be demonstrated by a WVP which failed to fall on occlusion of the long saphenous at the knee or the short saphenous at the popliteal space but which fell on occlusion of the vein at some point in the calf. Of the 21 extremities shown in Fig. 1 in which the pressure did not fall on saphenous occlusion at any point diseased deep veins were demonstrated by pathologic examination of the specimens on all of the 14 patients who received femoral vein ligation. Of the other 7, 3 had had femoral vein ligation performed elsewhere, 2 had no filling of the deep system by venogram and 2 had a suggestive history of phlebitis.

Diagnosis of Important Varices—The question often arises in the clinic as to whether varices which are not large or large veins which are not varicose are important enough to require surgical therapy. In a Veterans Hospital the motives which bring patients for treatment are often based more on the patient's realization that the treatment is free of charge than on the severity of his symptoms. Subjective cosmetic considerations also tend to magnify mild symptoms even in ex-soldiers. When we first tested such patients we hoped that a normal WVP of approximately 500 cm would give us assurance that even though the patient had prominent veins they were not important and surgery was not justified. This we have not found to be wholly true. Fig 8 shows the tests on 7 extremities whose WVP was within normal range. In these 7 extremities the symptoms although not severe were annoying and appeared due to varices. Furthermore in 6 instances they were improved by vein removal or ligation. It is to be noted in this group of pressures however that although the WVP was in the normal range they differ from the normal in that in 6 of the 7 the WVP50 represented an additional fall. Thus there is definite evidence of slight incompetency. In a

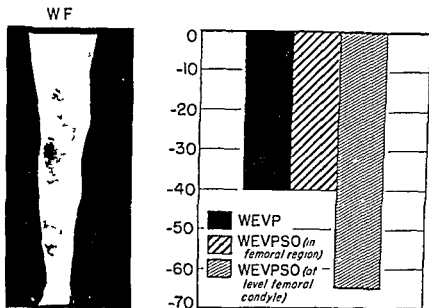


Fig 7—Varicose veins of right leg for 10 years. High saphenous ligation 4 years before admission. Symptomatic relief 2 years then recurrence. The test indicates an incompetent perforating vein in the thigh.

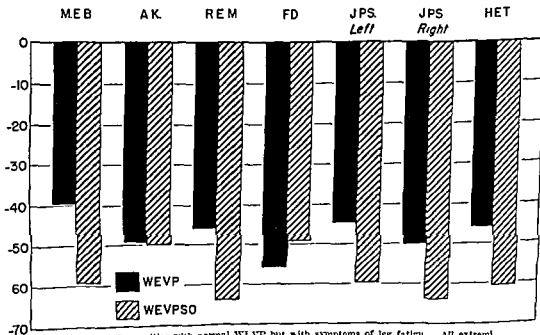


Fig 8—Extremities with normal WEVP but with symptoms of leg fatigue. All extremities except FD show an additional fall in pressure on walking when the saphenous vein is occluded.

normal extremity the fall on WFVP_{SO} is customarily less than on WFVP. We are permitted to state, perhaps, that however great a fall may be shown by the WFVP the vein is nevertheless partially incompetent if saphenous occlusion causes the pressure to fall still further.

In none of the extremities with small varicose or large nonvaricose veins the WFVP of which has been in normal range have there been complications namely edema or skin changes. We believe that the extremity which has an increased volume and weight of blood may have symptoms of fatigue even though vigorous walking may lower the pressure to normal levels. So long as such a pressure response is present, however, it is logical to believe that the extremity is insured against complications. This consideration might make a case for simple vein ligation without other procedure in elderly or debilitated patients in whom vein removal is feared because of the necessity of a general anesthesia or the possibility of a deep thrombosis. To support this is the very common history procured from patients who have recurrent symptoms following high saphenous ligation namely that the ligation relieved symptoms for a year or two before they recurred.

Of the patients with varicose veins whom we have treated a great many have had some structural skeletal defect. The most common of these has been pes planus. Others have been obesity, old fractures, and arthritis of the hip or knee. The presence of a relatively normal WFVP in many of these patients has served to emphasize the fact that factors which cause disordered mechanics may demand a priority for treatment which is at least equal to that of the varices.

Protection Against High Pressure Caused by Straining—Adams¹² observed that after saphenous vein ligation the pressure in the vein rose during straining to only one half the height that it did before ligation (114 mm. of mercury as compared with 224 mm. of mercury). We have made many attempts to test the effect of straining but have been unable to develop a satisfactory standard technique. Different individuals differ in their ability to hold their breath to exert a uniform straining pressure over a fixed time and to avoid using leg muscles which will cause pressure falls during the straining. Results on 30 tests were so variable that no accurate readings can be reported. Our impression is however, that the height of venous pressure attendant on straining in the resting erect position is more directly proportionate to the straining force exerted than to the degree of competency of the veins in the lower extremity. It is immediately obvious however that the extremity with normal veins can by muscular action reduce such pressures rapidly to or below normal after straining has ceased whereas the pressure in the extremity with incompetent veins reaches normal REVP only slowly after straining ceases and by definition falls little below that level. Thus the time that the increased pressures are at work is considerably greater in the latter instance. We do not believe that ligatures placed on main venous trunks act primarily as dams against excessive pressures from above. If they are beneficial at all in preventing the noxious effects of straining they do so by improving the general venous function of the limb.

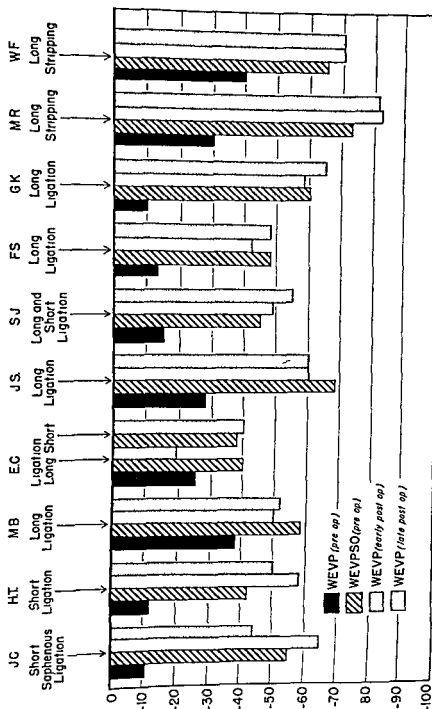


Fig 9—Walling venous pressure (mm Hg) before and after ligation or stripping of pure saphenous varices. J—C demonstrates that a high saphenous venous pressure was observed at the first ligation. The first ligation followed up 13 months after operation.

Therapeutic Considerations—During a 5 year period at the Veterans Administration Hospital at West Roxbury 302 patients with varicose veins were treated. Of these, 235 have been operated upon 67 were treated conservatively. Of those operated upon 260 extremities were involved 125 of which received simple ligation and 135 had part or all of the venous system removed by excision or stripping. Injections have been performed only in rare instances. Table I demonstrates the preoperative WFVP and WFVPSO in a selected group of extremities on which venous pressure determinations were made and compares this reading with the WFVP shortly after ligation or removal of the veins. In each case the predicted response occurred in the early postoperative period. FIG. 9 shows a group of tests performed 4 months or more after surgery and compares them with the early postoperative WFVP.

It is to be noted that the responses tend to be slightly better following stripping procedures than following ligation. Results following stripping or otherwise removing veins have been so satisfactory that the revival of this treatment by Linton¹¹ must be considered as a definite contribution. We now perform it in all patients with varices which are symptomatic or large. In small varices however we make a special point of searching carefully for structural postural or mechanical abnormalities which may be responsible for symptoms. If any are found they are corrected before the veins are removed.

TABLE I THE WALKING VENOUS PRESSURE TEST BEFORE AND AFTER SURGERY FOR DEEP VARICOSE VEINS

OPERATION	PREOPERATIVE		POST-OPERATIVE	DIFFERENCE BETWEEN WFVP PRE-OPERATIVE AND WFVPSO PRE-OPERATIVE
	WFVP	WFVPSO	WFVP	
Lig. high low	-8	-8	30	+38
Lig. high low hort	-27	-18	38	+65
Lig. high low	-10	-48	-4	14
Lig. high low hort	-23	-48	-18	+25
Lig. hort	-35	-22	-44	+11
Lig. hort	-11	-22	-40	+29
Lig. short	-22	-	-40	-18
Lig. high low hort	-	-41	-41	-42
Lig. high low hort	-7	-	-7	-11
Lig. high low hort	-13	-45	-49	-36
Lig. high low	-10	-40	-8	+2
Lig. high low	-1	-48	-4	+47
Lig. high low and excision	-28	48	-40	+10
Lig. high low	-28	48	-40	-12
Lig. short	-17	-48	-38	-21
Strip thigh h. calf	-4	-1	-1	-
Strip thigh h. calf	-1	-1	-1	-
Strip short	30	-	-18	-48
Strip short	-4	-7	-8	-3
Strip long	30	-49	-2	-79
Strip long	-40	-61	-70	-30
Strip long	14	-9	-60	-74
Strip long	48	-48	-30	-78
Strip long	-	-40	-40	-40
Strip long	30	-13	-8	-38
Strip long	1	-2	-2	-3
Strip long	4	-24	-22	-26

Lig. ligation

Strip stripping

The results following stripping as measured by the walking venous pressure test were more predictable while those following ligation alone

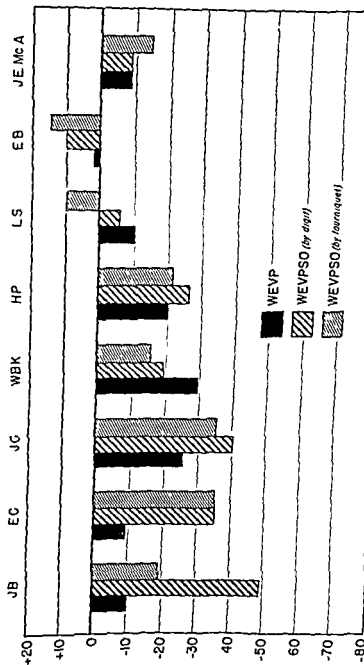


Fig 19.—Comparison of the performance of the three tests in 6 of the 8 extremities the venous pressure was measured by digital occlusion of the veins during digital occlusion of the veins.

Asymptomatic, medium or small varices can be left unmolested. Small varices which accompany postphlebotic stasis we also consider are better left alone unless the walking venous pressure test demonstrates that removal will be beneficial.

Walking venous pressure tests are not performed on all patients with varices. We confine them to patients in whom we desire to determine the competency of the deep system to those extremities which have recurrence after previous surgery, and to those whose symptoms are out of proportion to the extent of the varicose state. We consider that if walking venous pressure tests are not used the best method of testing is by the Perthes rather than by the Trendelenburg test. The former test is more functional. It is simpler to perform in that changes in position on the part of the patient are not involved. If it is used we consider distal occlusion to be a better method of cutting off the saphenous vein than a tourniquet around the thigh. Fig 10 demonstrates that a tourniquet around the thigh may not only in a postphlebotic extremity but also in a varicose extremity constrict useful venous return whereas the finger pressing on one of the main trunks does not.

SUMMARY AND CONCLUSIONS

- 1 The walking venous pressure test which measures the fall in pressure in the superficial veins of the lower extremity during walking is of great value in ruling out incompetency of the deep veins in situations where more conventional tests are difficult to evaluate.
- 2 In patients with pure varicosities of the superficial system it is also of value in mapping out sites of incompetency particularly where previous surgery has been done.
- 3 It is of help as an additional examination in demonstrating whether small varicose veins or large nonvaricose veins are symptomatic.
- 4 The test is not recommended for routine use in all uncomplicated saphenous varices.
- 5 Ligation or stripping of superficial veins gives postoperative pressure values which are predictable by preoperative tests.

REFERENCES

- 1 Edward F A and Edward J F. The Effect of Thrombophlebitis on the Venous Valve Surg. Gynec. & Obst. 60 710-720 1937
- 2 Human J. The Late Results of Femoral Thrombophlebitis and Their Treatment. New England J. Med. 235 247-253 1946
- 3 Homans J. Thrombophlebitis of the Lower Extremities. Ann. Surg. 87 641-651 1928
- 4 Thompson K W. Studies on the Relation of Dermatomyositis to Ulceration and Gangrene of the Extremities. J. Biol. & Med. 16 605-704 1944
- 5 Oberner A and DeBakey M. The Use of Valvulation in the Treatment of Venous Thrombosis. Surg. Gynec. & Obst. 84 659-664 1947
- 6 Blacklock A. Oxygen Content of Blood in Patients With Varicose Veins. Arch. Surg. 19 898-905 1921
- 7 Delbet P. Du rôle de l'insuffisance valvulaire de la saphène interne dans les varices du membre inférieur. Semaine mèd. 17 31- 1907
- 8 Trendelenburg F. Ueber die Unterbindung der Vena saphena magna bei Unterschenkelvaricen. Beitr. z. klin. Chir. 7 195-210 1890
- 9 Perthes G. Ueber die Operation der Unterschenkelvaricen nach Trendelenburg. Deutsche med. Wochenschr. 21 232-27 1895

- 10 Beecher, H. K. A Study of the Flow of Blood in the Free and Localized Sustained High Venous Pressure as Found With Varices of the Great Saphenous System During Walking. *J Clin Investigation* 16 737-739, 1937
- 11 Buro A. Ueber Blutdruck und Blutkreislauf in den Krampfaderen der unteren Extremitäten. *Acta chir Scandinav* 80 1181 1934
- 12 Adams John C. Physiological Factors in Various Venous of the Lower Extremities. *Surg Gynec & Obst* 69 717-725 1939
- 13 Veal J. R. and Huey H. H. The Use of "Exercise Tests" in Connection With Venous Pressure Measurements for the Detection of Venous Obstruction in the Upper and Lower Extremities. *Am Heart J* 20 308-321 1940
- 14 Linton R. R. Surgery of the Veins of the Lower Extremity. *Minnesota Med* 32 74-41 1940
- 15 Warren L. White L. A. and Ichler C. D. Venous Pressure in the Saphenous System in Normal Varicose and Postphlebotic Extremities. Alterations Following Femoral Vein Ligation. *Surgery* 26 435-445 1949
- 16 Mahorner H. Infarcted Leg and Leg Ulcers. A Clinical Study of Their Etiology and Treatment. *Surg Gynec & Obst* 88 115-124 1949

DISCUSSION

DR. J. ROSS VAIL.—I agree with Dr. Warren that the commonly used "tourniquet tests" for determining the competency of the venous circulation of the lower extremities are too often inconclusive. Dr. Hugh Huey and I have demonstrated that many patients with venous insufficiency were in a state of compensation during rest and in the supine position and that a compensation occurred only during functional positions and exercise. At that time we devised a method of determining the venous pressure changes in the deep and superficial veins during exercise in the erect position. A characteristic declining curve was obtained in the normal subject for the deep and superficial veins. An entirely different curve was demonstrated when there was obstruction or valvular incompetency of the major veins. In this group the pressure rose during exercise and slowly returned to the base line during rest. When deep venous insufficiency existed we found intravenous pressure determination of the superficial veins give a wide fluctuating curve; however when a tourniquet was applied about the thigh to constrict the superficial veins then we obtained the typical insufficiency curve.

In questionable cases we have been able to differentiate edemas of the extremities due to venous insufficiency from the nonvenous forms.

Now Dr. Warren has further demonstrated that venous pressure measurements made in the erect position and during walking provide the most accurate test for even mild incompetency of the deep veins. His application of this test in determining the type of treatment needed is most interesting.

I am sure this test will find a most valuable application in the evaluation of the venous circulation in compensation cases. The usual tests and even venograms have too often given the wrong impression and some patients who are entitled to a disability rating have been classified as having adequate venous circulation. Through the use of the walking venous pressure test as illustrated by Dr. Warren a correct evaluation of the venous circulation can now be determined.

A FOLLOW UP STUDY OF PATIENTS WITH THROMBOANGITIS OBLITERANS (BUERGER'S DISEASE)

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DURING the period 1934 to 1948 inclusive a diagnosis of thromboangitis obliterans (Buerger's disease) was made on 283 patients at the University Hospital. It was felt desirable to study these patients in the form of a follow up analysis in an attempt to evaluate the result of the various forms of therapy which had been employed and more important to determine the ultimate prognosis in comparison to other previously reported series of patients with this disease.^{1, 2, 3}

Of the total number of patients on whom the diagnosis of thromboangitis obliterans had been made 149 were ultimately selected on the basis that they fulfilled the accepted criteria and had an adequate record in which sufficient data such as a pathology report on removed tissue was available further to substantiate the original impression. The original diagnosis had been excluded in a large number of these patients by examination at a later date, death with autopsy analysis, etc. In some the presence of all peripheral pulses and the absence of the usual signs and symptoms of thromboangitis obliterans mitigated against this diagnosis. The disease was undoubtedly present in some of the excluded patients in this series but certainly in a small minority.

Of those patients selected for study (149) a 100 per cent follow up analysis was achieved through a written reply to a questionnaire sent to and obtained from the patient (if living) from friends or relatives (if dead including death certificate reports) and in many instances return visits to the outpatient clinic for examination and evaluation. The factual data recorded in each case were of such a nature as to allow a complete review of the course of the patient's disease and response to various forms of therapy prior to, during and subsequent to study and treatment at the University Hospital.

GENERAL DATA

Of the 149 patients in this series 147 were males and 2 were females. In the latter 2 cases pathologic confirmation of the diagnosis was obtained. Only 1 patient in the entire series had diabetes mellitus and only 20 (13.6 per cent) of the patients were Jewish. The extremities involved by thromboangitis obliterans during the course of the patient's disease were as follows. In 123 patients the lower extremities alone were involved. Of these 70 developed the disease bilaterally, 28 had involvement of the right lower extremity, 25 of the

¹Presented in part at the third annual meeting of the Society for Vascular Surgery, Atlantic City, N. J., June 5, 1949.

²This work was aided by a grant from the John Harper Seely Fund for Medical and Surgical Research.

³Attending Surgeon, Alexander P. H. Hospital, Detroit, Mich., and Former Assistant Professor of Surgery, University of Michigan, Ann Arbor, Mich.

left lower extremity. In 22 patients the disease was present in an upper extremity in addition to the lower extremity. In 2 patients the right upper extremity alone was the site of the disease, in 1 patient the upper left extremity and in 1 other patient the vascular involvement was present in both upper extremities and absent elsewhere. In 5 cases a definite family history of Buerger's disease was obtained.

These figures are strikingly similar to the pattern of the disease as originally reported by Buerger⁵ with the exception of the racial incidence.

The average age of onset of the disease in the patients in this series was 34.9 years with the youngest patient giving a reliable history of onset at the age of 15 years. The oldest age of onset of symptoms was 53 years and in this patient the signs, symptoms, and findings were so classical that despite the possibility of a mixed form of vascular disease he was included in this series. In the follow up analysis however it was found that the statement of the patient as to the exact year of onset varied with that reported in the record of the patient. It was the impression of the authors that the disease in many cases had its onset at a time interval earlier than that reported by the patient.

These patients when first seen, had an average age of 35.3 years. There was an average of 3.8 years between the onset of symptoms and the time they were first seen at the University Hospital. All patients were referred by other physicians. In 2 instances in the follow up analysis, the patient had visited over 100 different physicians during the course of his illness.

SIGNS AND SYMPTOMS

Classical signs and symptoms of arterial occlusive vascular disease were present in practically all of the patients in the series being reported inasmuch as they represented a rather well advanced group with thromboangitis obliterans. Many of the patients had been previously hospitalized the largest number of admissions to a hospital for a single patient being 36.

Coldness of the involved extremity, symptomatic or clinical, was present in 126 of the 149 patients at some time in the course of their disease. This symptom and sign was absent in 16 patients and no record was obtained in 7 others. Raynaud's phenomena was present in 24 cases and could be elicited by exposure to ice water in every instance. All 24 of these patients had well established organic changes in the digits and definite evidence of occlusive arterial disease.

Pain in the involved extremity was present in 143 of the 149 patients. It was absent in 4 cases and no record was obtained in 2 cases. The pain was usually classified as constant, intermittent, nocturnal, rest pain, paresthesia, or pain of a neuritic type. Constant pain and severe rest pain appeared to contribute significantly to a poor prognosis inasmuch as this type of pain was present in practically all patients undergoing a major amputation. Pain relieved by local nerve block and/or sympathetic block in most instances responded favorably to treatment.

Intermittent claudication, one of the most helpful criteria in establishing the diagnosis, was present in 149 patients.

a figure in keeping with the more frequent site of involvement in the lower extremities and the well advanced state of the disease present in the patients in this series

Ulceration of a digit foot leg, or amputation stump was present in 74 instances. Frequently, the ulceration was the site of previously established gangrene or had developed following amputation of a phalanx or digit. There was an associated infection deep or superficial in 76 instances an ulcer being present in most but not all of these patients. Surface involvement by superficial infection was present in 29 patients infection of the deeper tissues (spreading) in 12, and in 20 clinical and roentgenologic evidence of osteomyelitis which varied greatly in severity and extent.

Established gangrene of an involved part was present at the time of admission in 45 of these patients. The extent and location of the gangrenous process varied from a dry minute involvement of a digit to massive moist gangrene of a foot. In those patients with a dry gangrene of limited extent in a digit the prognosis held favorably while under continual care. The outlook over the entire course of the disease in such instances was unfavorable and particularly so if the patient continued the use of tobacco in any form or failed to return to his physician frequently for observation and care. In the interval 1940 to 1948 inclusive it was found necessary to perform a major amputation of an extremity (foot or leg) at the University Hospital in only 6 instances. In 4 of these 6 patients the disease was beyond conservative management at the time of admission and in the remaining 2 instances sympathectomy had been performed as a last chance gesture for far advanced thromboangitis obliterans with gangrene. In the last 3 years of this study no major amputation for Buerger's disease was performed. In the last 8 years if the condition of the patient allowed conservative management at the time he was seen major amputation was practically never necessary while the patient remained under rigid supervision.

Visceral involvement by thromboangitis obliterans has been reported at infrequent intervals and proved in extremely few instances. Suggestive but not proved evidence of visceral involvement was present in 13 of the patients in this series. These included (by location) 1 renal 17 cardiac 7 splanchnic 5 ophthalmic 13 cerebral. Since the evidence was inconclusive in every instance little importance other than the tendency to have "vascular" involvement can be attached to these figures.

SUPERFICIAL MIGRATORY PHLEBITIS

The incidence of superficial migratory or nodular phlebitis was 50.7 per cent in this series of 149 patients 76 patients having either definite clinical findings history or pathologic confirmation. This incidence is somewhat higher than other reported series but may merely reflect the exclusion of patients from the series in whom the diagnosis of Buerger's disease was considered doubtful and the inclusion of those patients who fulfilled rather rigid criteria. The upper extremity was the site of involvement in 5 patients the lower extremities in 62 and 9 patients had superficial phlebitis involving both upper and lower extremities (Table I).

Of somewhat greater significance was the finding that definite superficial migratory phlebitis preceded the signs and symptoms of arterial occlusion in 16 patients coincided with the onset in 46 patients, and followed the development of vascular occlusion (arterial) in 12 others. The time interval relationship could not be determined in 2 instances. The phlebitic manifestations were found to precede the signs and symptoms of arterial occlusion in 16 patients by an interval as short as 6 months and as long as 72 months. On the other hand some patients did not develop any phlebitis manifestations for an interval of 30 years after the manifestations of arterial occlusion. The important point to be made it would seem, is that in a young male patient with superficial or nodular phlebitis careful consideration should be given to the possibility that the patient is potentially a candidate for Buerger's disease. In such an instance an early diagnosis and careful follow up would be well rewarded by a satisfactory result of treatment.

TABLE I. SUPERFICIAL PHLEBITIS INCIDENCE

Total patient	149				
Patients with phlebitis	6				
Upper extremity				3	
Lower extremity				60	
Both				4	
					16
					46
					12
					2
of superficial migratory thrombo					

The superficial phlebitic process in most instances served as an excellent guide to the activity of the underlying vascular occlusion. The presence of superficial phlebitis did not mitigate against a good prognosis with the exception that in those patients in whom frequently recurring crops of phlebitic nodules tended to develop persist and migrate the outlook concerning major amputations was poor in every instance in the ultimate follow up analysis.

PROGNOSIS WITH RESPECT TO AMPUTATION

In the 149 patients subjected to a follow up analysis (1934 to 1944) 64 patients (43 per cent) were found to have submitted to one or more amputations during the course of their disease. Although this figure at first glance is not greatly at variance with the analysis of Horton in 1938 which would suggest that the prognosis as measured by amputation had not greatly changed in the past decade more critical analysis of true relationship demonstrates that considerable improvement in the prognosis has been obtained. Horton in a study of 948 separate patients with Buerger's disease followed between 1907 to 1937 (80 per cent follow up analysis) found that 401 of these patients underwent amputation and that 69 per cent of the amputations involved the loss of a major portion of the extremity (foot leg hand). Between 1918 to 1927 71 per cent of the amputations were major in nature. 1928 to 1937 63 per cent, and 1933 to 1937 45 per cent so that a definite improvement in prognosis based on ampu

tation had occurred. He also found that during the first 3 years of the disease 694 patients had 215 amputations (31 per cent) and 69 per cent did not require amputation. During the first 5 years of the disease 628 patients had 248 amputations (39.5 per cent) and 60.5 per cent did not require amputation. During the first 10 years of the disease 334 patients had 202 amputations (59.9 per cent) and only 40.1 per cent escaped amputation.

Silbert (1935)² reported a much more favorable prognosis with respect to amputation in a personal series of 124 cases followed over a 10 year interval. The incidence of amputation being 7.6 per cent. In a previous survey by Silbert (1930) 464 patients followed in the first 5 years of their disease demonstrated that 64 per cent had undergone an amputation. He later estimated that under any circumstances amputation was apparently unavoidable in about 35 per cent of all cases. Silbert² also recorded the remarkable observation that in 309 patients followed 2 to 10 years no amputations were necessary if the patient had discontinued smoking.

In the present series the patients undergoing amputations were divided into three groups for more critical analysis (Table II). Group II comprised 25 separate patients undergoing some form of amputation at the University Hospital and in addition 6 patients from Group I. Group III comprised 16 patients having their amputations done elsewhere after leaving the University Hospital in addition to 10 patients from Groups I and II. Thus a total of 68 patients participated in the amputation group one or more times, the greatest number of amputations in a single patient being 34 and 30 in 2 instances. Table III

TABLE II MAJOR AMPUTATION DATE AND INCIDENCE¹

	GROUP I (PRIOR)	GROUP II (UNIVERSITY HOSPITAL)	GROUP III (ELSEWHERE)
1930 to 1939	1	2	—
1939 to 1944	2	0	—
1945 to 1950	4	6	9 (40% entire group)
1940 to 1944	—	4 { (40% entire entire 14) 11 14 2% major amputations (4% major amputations)	2
1945 to 1949	2	—	5
Patients	10	14	16

¹Refer to primary procedure involving 39 separate patients. An secondary procedure involving 10 of 39 patients.

²Major amputations in 39 separate patients. Note that in the interval 1930 to 1939 4 per cent of the entire group participated.

No major amputation last year at University Hospital.

TABLE III PATIENTS UNDERGOING AMPUTATIONS

	PRIOR TO BEING SEEN GROUP I (2%)	UNIVERSITY HOSPITAL GROUP II (10 & 6)	SUBSEQUENT ELSEWHERE GROUP III (10 & 10)
Fingers	—	3	6
Toe	11	1	—
Foot	—	0	0
Legs	10	14	10
Arms	0	0	1

Amputation carried out prior to entering and subsequent to therapy at the University Hospital. The figures listed under the various groups include separate patients plus those participating from the previous group.

Of somewhat greater significance was the finding that definite superficial migratory phlebitis preceded the signs and symptoms of arterial occlusion in 16 patients coincided with the onset in 46 patients and followed the development of vascular occlusion (arterial) in 12 others. The time interval relationship could not be determined in 2 instances. The phlebitic manifestations were found to precede the signs and symptoms of arterial occlusion in 16 patients by an interval as short as 6 months and as long as 72 months. On the other hand some patients did not develop any phlebitic manifestations for an interval of 30 years after the manifestations of arterial occlusion. The important point to be made, it would seem, is that in a young male patient with superficial or nodular phlebitis careful consideration should be given to the possibility that the patient is potentially a candidate for Buerger's disease. In such an instance an early diagnosis and careful follow up would be well rewarded by a satisfactory result of treatment.

TABLE I SUPERFICIAL PHLEBITIS INCIDENCE

Total patients, 149	
Patients with phlebitis	76
Upper extremity	5
Lower extremity	60
Both	9
Preceding the signs and symptoms of arterial occlusion	16
Coincident with vascular occlusion	46
Following vascular occlusion	12
Not determined	2

Data relevant to the incidence and time of occurrence of superficial migratory thrombophlebitis in patients with thromboangiitis obliterans

The superficial phlebitic process in most instances served as an excellent guide to the activity of the underlying vascular occlusion. The presence of superficial phlebitis did not mitigate against a good prognosis with the exception that in those patients in whom frequently recurring crops of phlebitic nodules tended to develop persist and migrate the outlook concerning major amputations was poor in every instance in the ultimate follow up analysis.

PROGNOSIS WITH RESPECT TO AMPUTATION

In the 149 patients subjected to a follow up analysis (1934 to 1948) 65 patients (43.6 per cent) were found to have submitted to one or more amputations during the course of their disease. Although this figure at first glance is not greatly at variance with the analysis of Horton in 1935 which would suggest that the prognosis as measured by amputation had not greatly changed in the past decade more critical analysis of true relationship demonstrates that considerable improvement in the prognosis has been obtained. Horton in a study of 348 separate patients with Buerger's disease followed between 1907 to 1937 (80 per cent follow up analysis) found that 401 of these patients underwent amputation and that 69 per cent of the amputations involved the loss of a major portion of the extremity (foot leg hand). Between 1918 to 1927 71 per cent of the amputations were major in nature. 1925 to 1937 63 per cent and 1933 to 1937 48 per cent so that a definite improvement in prognosis based on ampu

TABLE IV FOLLOW-UP ANALYSIS OF PATIENT WHO UNDERWENT SYMPATHECTOMY AT SOME TIME IN COURSE OF THEIR DISEASE

	TOTAL	UNIVERSITY HOSPITAL	FISWHIFF
Patients	38	31	7
% series	100%		
Value of sympathectomy			
Good	(14)	13	1
Fair	(24)	18	6
Poor			
Amputation necessary	16 (42.1%)	10 following operation	
Result			
	Prior to 1937	1937 to 1940	1941 to 1945
Good		1	8
Fair	2		4
Poor	1	5	5
Total	3	16	17
			38

2 years, was selected as representing the period during which the operative procedure should have allowed the patient better development of collateral circulation and fewer painful complaints with reference to the disease.

On such a basis 14 of the 38 patients evidenced a very satisfactory response to their sympathectomy and the remaining 24 a fair or poor response. Ultimately, in the course of the disease 16 of the 38 patients (42.1 per cent) lost a portion of an extremity by amputation although all of these were not necessarily related to the area previously sympathectomized. Ten patients underwent amputation relatively soon after the sympathectomy.

Such factual data do not necessarily represent the results of sympathectomy in patients with Buerger's disease because of the large number of modifying or qualifying factors present in each case.

In the opinion of the authors many of the procedures were performed much too late in the course of the disease not occasionally as a last chance gesture for the patient and occasionally in patients not under good management.

In our own opinion the choice of performing a sympathectomy in patients with thromboangitis obliterans should be primarily related to the course of the disease that is the race between episodic progressive vascular occlusion on the one hand and the development of collateral vascular channels on the other hand. Given a sufficient time interval of freedom from further vascular occlusion or an enhanced development of circulation in the smaller vessels following operation then the patient should demonstrate obvious benefit. The judgment as to the time at which a sympathectomy should be performed will then obviously be modified by the experience of the surgeon and other factors. If sympathectomy is to be of value in saving part or the whole of an involved extremity it is our opinion that it should be performed early in the course of events and that in addition a bilateral procedure should be given every consideration.

In addition since the vascular lesion in thromboangitis obliterans tends to involve large and medium sized vessels it is logical to assume that if large or medium sized collateral channels are established early (and certainly this would be influenced by sympathectomy) the extent of the vascular occlusion in turn would have to be greater to produce a vascular insufficiency in the extremity.

illustrates the data with respect to the part involved time of amputation etc. A reanalysis of the data was of interest in that for the patients coming under our own care and requiring amputation only 10.06 per cent of the entire series participated. Further, if we exclude those individuals who had an amputation prior to visiting the University where additional procedures were necessary, this figure drops to 7.38 per cent. In other words, where the use of conservative procedures was possible, the prognosis was very favorable in our own experience with the patient.

Furthermore, an analysis of the year in which the amputations were carried out was of some interest. For this purpose, only major losses of a part were included. Table II illustrates the fact that in the years 1945 to 1948, only two major amputations were necessary and that between 1940 to 1948 only 6 cases required major amputations or 4.02 per cent. All of these occurred in addition, in individuals already beyond aid of conservative measures when first seen. Such an analysis, however, does not change the over all amputation rate for the entire series (45.6 per cent for all amputations, 26.03 per cent for major amputations) when consideration of prior and subsequent treatment is considered. Of considerable importance, however, is the marked lowering of the amputation incidence when such patients are treated intensively by an interested group of physicians in one institution. Such a deduction is supported by the reports of Silbert and Allen⁴ and others. In addition, within the past few years (1940 to 1948), the incidence of major loss of a part has steadily declined although the majority of patients with *thromboangitis obliterans* in this series were seen during this interval. The addition of chemotherapeutic and antibiotic agents to the therapy being employed has undoubtedly lessened the number of secondary amputation procedures following the removal of a phalanx or digit because of the superior control of attendant infection. These agents have also prevented in many instances the development of gangrene secondary to infection.

Lastly, it is becoming more apparent just as in the patient with arterio-sclerotic gangrene that the senior surgeon should concern himself more with the local amputation procedure (digit) and less with the supracondylar removal of the extremity. Experience and precise judgment in the removal of a digit may preclude a later necessity for higher amputation.

ANALYSIS OF PATIENTS WHO UNDERWENT SYMPATHECTOMY

Thirty eight of the 149 patients (25.5 per cent) in this series underwent either lumbar dorsal or a combined sympathectomy, the largest number being of the lumbar type (Table IV). Thirty one of these procedures were carried out at the University Hospital, and 7 were done elsewhere. In this analysis the value derived from this operative procedure was arbitrarily classified as good or excellent if relief of major symptoms occurred and amputation was not necessary over a 2 year interval or longer; fair if the majority (but not all) of the major symptoms were for the most part alleviated and major amputation was not necessary during a 2 year interval or longer; and poor if symptom abatement failed to occur or loss of a part was necessitated. It is realized that such a classification is distinctly an arbitrary one. The time interval chosen

from death certificates, the data obtained were in general in keeping with previously reported observations.⁴ Seventy five per cent of the 28 deaths resulted from some form of vascular disease or its complications including coronary thrombosis, unspecified heart disease, apoplexy, pulmonary embolism etc. The remaining deaths were attributable to suicide (3) cancer, and other unrelated causes. In general, the tendency of these patients to develop other types of so called vascular lesions was noticeable.

A detailed analysis of the average age and duration of the disease in the patients dead on follow up was of some interest (Table VII) in that the average duration of the disease when the patient was first seen was identical to that of the patients still living (39 years). The average total duration of the disease however was 832 years the average age at death being 43.71 years or approximately 5 years greater than the average age in the entire series. The relatively young average age at death would appear to be in keeping with the tendency of these patients to develop other vascular lesions. No proof was obtained in any instance that visceral involvement by thromboangitis obliterans was the cause of death.

TABLE VII ANALYSIS OF 28 DEATHS IN A SERIES OF 149 PATIENTS WITH THROMBOANGITIS OBLITERANS

Deaths in series	28 (18.7%)
Average age at time of death	43.71 yr
Average age at first visit	39.25 yr
Average duration of disease at first visit	3.90 yr (2.9_ if we exclude 1 patient 30 yr)
39.25 yr	3.90 yr
Average age onset entire series	34.4 yr
Average duration when first seen (149)	3.9 yr
191 living patients age of onset	3.37 yr
121 living patients duration disease when first seen	3.70 yr

GENERAL DISCUSSION

A statistical analysis of patients with thromboangitis obliterans while of interest from the viewpoint of prognosis fails to bring to light in numerical fashion many of the more important features of the disease and the type of patient in which it occurs.

In the present series a firm impression of the importance of psychosomatic factors, both from the standpoint of etiology and perpetuation of the disease was obtained. This was felt to be of sufficient importance to warrant a separate report on this phase of the disease. Many of the patients were frequently married and divorced, many exhibited a belligerent bellicose type of personality with a noticeable tendency to refuse to carry out in detail the advice of the physicians they consulted. The data relevant to the use of tobacco are of interest in this respect. Several of the patients had developed drug addiction which was exceedingly difficult to control. It appeared to us that patients with Buerger's disease are more prone to have accidents with resultant injury to the extremities than the average individual. Many of the patients had recurrent

DATA RELEVANT TO THE USE OF TOBACCO

One of the most important, if not the most important, measures in the treatment of occlusive peripheral vascular disease is the cessation of the use of tobacco in any form by the patient. Silbert has reported the interesting observation that he has never seen a patient with Buerger's disease who did not use tobacco in some form. In the present series of 149 patients only 1 recorded and verified instance of the patient never having used tobacco was obtained (Table V).

TABLE V DATA RELEVANT TO THE USE OF TOBACCO (130 RECORDS)

Number of patients in series	149
No record of use of tobacco	3
Record of never using tobacco	1
Follow up Analysis	
Completed	99

On the follow up analysis 33 patients reported in writing that they had ceased smoking. Of the 121 living patients 88 still used tobacco in some form despite the repeated admonitions they had received from various physicians during the course of their illness. Five patients (dead on follow up) had continued smoking prior to their death. Of the 33 patients who had ceased smoking practically all had experienced satisfactory progress in the amelioration of the disease with long intervals between periods of further episodic vascular occlusion. The amputation incidence in these non smoking patients following the cessation of smoking was negligible.

Such findings are merely in keeping with the previously reported findings of other authors.^{2, 6} Maddock, Malcolm and Collier have also reported the interesting observation that cigarette smoking by Jewish males produces a greater change in skin temperature than in gentile males which might account for the greater prevalence of thromboangiitis among Jews than other elements of the population.

The cessation of smoking in patients with vascular disease obviously needs further emphasis.

ANALYSIS OF 28 DEATHS IN A SERIES OF 149 PATIENTS WITH
BUERGER'S DISEASE

Twenty-eight of the 149 patients were reported dead on follow up analysis (Table VI). Although the exact cause of death was obtained in many instances

TABLE VI CAUSE OF DEATH 28 PATIENTS

CAUSE OF DEATH	
Death due to vascular disease	
Accidental death suicide	3
Cancer of lung	1
Rectal fistula, appendectomy	1
Pneumonia nephritis	2
Total	28

I think the diagnosis of Buerger's disease is made too often. It is a disease of relatively young adult beginning almost always by the thirties the average age of Dr Campbell's series being about 35 years. It is seldom I think, that one should make the diagnosis of Buerger's disease when a patient has the onset of symptoms after 45 years of age since only rarely does Buerger's disease begin after that time and one should then think of the much more common peripheral arteriosclerosis.

Occasionally, arteriosclerosis will begin before 45 but usually there are other indications in the patient of a degenerative cardiovascular lesion such as hypertension, coronary disease or apoplexy. I use the onset age of 45 as a rough dividing line in considering the differential diagnosis of Buerger's disease or arterio sclerosis. Of course there are other symptoms and signs that help to distinguish between the two diseases.

Whatever the diagnosis is the patient with chronic peripheral arterial deficiency will be difficult to treat and it will be necessary to use every means at hand to save an extremity or return the individual to a useful living. These individuals are just as crippled as the patient with heart disease.

I agree that sympathectomy should be considered as conservative treatment in the handling of peripheral vascular deficiency. I do not believe that the commonly employed tests of typhoid injection or peripheral nerve block or a sympathetic block should be the only indicator in deciding whether a sympathectomy will be of value in a patient with a threatened limb loss and I am willing to advise the operation on patients even when the tests are not too favorable feeling that we have to add everything we can to save even parts of the extremities of the individual.

I think a sympathectomy a lumbar sympathectomy at least can be classed under conservative treatment and certainly if it is done through a lateral muscle splitting approach the patient has very little disability. Patients do lose limbs after a sympathectomy but some are saved. In the past we have employed this operation in the worst cases but now there are several series in which the procedure has been employed much earlier and the result are better.

Concerning tobacco a good many years have gone by since Dr Coller and I first showed with kin temperature studies that as a result of smoking a decrease occurred in the blood supply of the extremities particularly in the fingers and toe. In these patients with a vascular deficiency in the lower extremities it is the toes that commonly give difficulty. They are stuck out from the more solid foot and are easily traumatized by all sitting shoes or cold. Once injured any further loss of blood supply as by smoking is a very serious factor and that is exactly what tobacco will do in the disease.

Some men claim that tobacco is the cause of Buerger's disease particularly emphasizing its vasoconstrictor effect or possible allergic action. Whatever the cause I do know that Silbert has said that he has never known a patient with Buerger's disease who has recovered from an acute deficiency to get worse unless he continued to smoke and Silbert in New York City has had a tremendous amount of experience in handling these patients.

I do not know of any other disease in which there is such clear evidence that tobacco is harmful, and as far as I am concerned I am not willing to treat or worry about a patient with Buerger's disease who keeps on smoking. This may be easier for me to say because I do not smoke. Some of you men who smoke may have more trouble in advising against smoking. But the fact remains that it has a terrifically harmful effect on the patient. They must be thoroughly warned and understand that if they continue to smoke they are going to have more trouble with Buerger's disease. It often seems to be a choice of their legs or their tobacco.

episodes of phlebitis or further vascular occlusion while under obvious stress from environmental factors, such as difficulties at home financial worries lack of employment, etc

While such features do not lend themselves readily to statistical analysis they do represent an important series of impressions obtained from an analysis of the entire course of the disease in a carefully surveyed group of patients with Buerger's disease

SUMMARY

1 A 100 per cent follow up analysis of 149 patients with thromboangitis obliterans is reported

2 The ultimate prognosis, based on amputation was not greatly different than in previously reported series (45.6 per cent) when consideration was given to treatment previous to being seen and subsequent to discharge

3 Superficial migratory thrombophlebitis may precede the clinical development of occlusive arterial lesions in these patients

4 It would appear that if sympathectomy is to be employed in treatment it should be carried out early in the course of the disease

5 While these patients remain under rigid supervision by an interested group of physicians the prognosis appears to be very favorably influenced, the percentage of patients having major amputations being reduced to a minimum. No major amputations were necessary in the last 2 years of this study at the University Hospital although a considerable number of these patients were treated during that interval

6 The large majority of the living patients on follow up analysis had failed to cease using tobacco

7 Psychosomatic factors appear to play a definite role both in the etiology and the perpetuation of the disease

8 More exact criteria for amputation and sympathectomy are desirable in patients with thromboangitis obliterans. The dissemination of such information is of paramount importance in the treatment of patients with this disease

REFERENCES

- 1 Horton B. T. The Outlook in Thrombo Angitis Obliterans J. A. M. A 111 2184 2189 1934
- 2 Silber Treatment of 54 Cases by 1000 cc of Ten
- 3 Silber ted Injections
- 4 Allen, ses Philadel
- 5 Buerger, Vaso
- 6 Madd pany 63 pp bliterans and

DISCUSSION

TABLE I RESULTS OF VARIOUS AUTHORS WITH SYMPATHECTOMY FOR RAYNAUD'S DISEASE

	RESULT			
	CASES	GOOD	FAIR	FAILURE
Adson and Brown 1933	4	—	0	—
Telford 1944	3	16	8	13
White and Smithwick 1941	93	60	27	5
Kinmonth 1949	73	52	8	13

Extremities

TABLE II

AGE GROUP (YEARS)	NUMBER OF PATIENTS
10 to 20	4
20 to 30	10
30 to 40	13
40 to 50	8
50 to 60	5
Total	40

II In view of the small number of cases in each age group it was thought unwarranted to attempt a correlation between age and recurrence rate

The clinical history and the past and present physical findings were carefully scrutinized but for the purpose of the clinical aspects of this report only the evidences for clinical recurrence of vasospasm have been used This consisted of a history of blanching or cyanosis upon exposure to cold outside the hospital or when exposed to cold in the laboratory In addition the patients were tested in the laboratory for objective signs of recurrence Vasomotor activity was tested by exposure of the patients to an environmental temperature of 65 to 68° F Failure of the digital skin temperature to drop below 90° F after exposure to this degree of cold for one hour was taken to indicate lack of vasomotor activity When the skin temperature did drop below 90° F in the digits the possible direct effect of cold upon the blood vessels was ruled out by appropriate peripheral nerve block A rise in temperature of the skin after such a nerve block was interpreted as indicating a release of vasomotor nerve activity Skin temperatures were recorded automatically by means of an eight lead electronic potentiometer each lead recording in rotation at intervals of 4 minutes Two leads were used for consecutive recording of the environmental temperature All studies were done in a controlled temperature room Reflex vasodilatation and plethysmography were also done under the same conditions but they added nothing to the present discussion and are therefore not considered in this report Sudomotor activity was tested by exposing the patients to an environmental temperature of 110 to 120° F for one hour or more and then measuring the skin resistance by means of a potentiometer²⁴

RESULTS

The effectiveness of sympathectomy will be considered separately for upper and lower extremities since the results for the two regions are so different

Upper Extremities

1 *Over-all Results of Sympathectomy for Raynaud's Disease of the Upper Extremities*—Seventy five upper extremities were examined in thirty eight pa-

EVALUATION OF SYMPATHETIC NEURECTOMY IN RAYNAUD'S DISEASE

BASED ON A FOLLOW UP STUDY OF FORTY PATIENTS

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THE observations of Royle²³ in 1924 that coldness and sweating of the skin disappeared after regional sympathectomy suggested a new approach to the treatment of vasospastic diseases of the extremities. In 1925 Adson and Brown² demonstrated by means of calorimetry as well as by skin temperature studies that vasospasm of the lower extremities was relieved by lumbar ganglionectomy and iliac periaxillary sympathectomy. In the quarter century which has followed this pioneer work, release of the arterial tree from control by the sympathetic nervous system has become a popular form of treatment for Raynaud's disease and other forms of arterial vasospasm.

The results, however, have not been uniformly successful (Table I). Even the earliest case report, with a follow up of one year suggested two of the problems which are foremost at the present time.² First recurrence took place in that patient within one year after ramisection. Second, the clinical result was better in the lower than in the upper extremity. This experience became commonplace.^{2, 4, 10, 15, 19, 20, 31, 34, 35, 38}

In spite of considerable clinical work on the problem and the development of several different types of operation,^{1, 24, 31, 33, 35} the questions related to recurrence after sympathectomy for vasospasm in the upper extremity remain unanswered. In addition, the recent popularity of drugs which block the action of the vasomotor component of the sympathetic nervous system raises the question of other than surgical therapy in vasospastic diseases of the extremities.^{1, 33} For these reasons it was thought desirable to present objective postoperative data obtained in a general study of patients with Raynaud's disease for whom various types of sympathectomies had been done 6 months to 20 years previously.

METHOD

This report is based on patients operated upon in this hospital since 1929 for Raynaud's disease or Raynaud's phenomenon and who were available for a full day's examination in the peripheral vascular laboratory. There were 40 patients found available and studied. Thirty eight of these had sympathectomies of the upper extremity (75 extremities), 2 had lumbar sympathectomies only and 16 patients had both lumbar and dorsal sympathectomies. Patients who had been operated upon for less than 6 months of the time of this report have been excluded from the analysis.

No selection was made on the basis of age of the patients. The distribution among the different age groups at the time of operation is represented in Table

Read at the third annual meeting of the Society for Vascular Surgery, Atlantic City, N. J., June 5, 1949.

tients and the clinical results were evaluated. These data are presented in Fig 1. The category "Clinically Cured" represents those extremities in which attacks of vasospasm had not occurred after operation and could not be precipitated in the laboratory upon exposure to cold. The category "Clinically Improved" includes those extremities in which attacks of vasospasm did occur after sympathectomy, but the patients stated at the time of examination that they were better than they had been before sympathectomy. Individuals who stated that they were improved temporarily by operation but were not any better than before operation at the time of the examination were not included in the category of "Clinically Improved."

RESULTS OF SYMPATHECTOMY IN RAYNAUD'S DISEASE OF THE UPPER EXTREMITY

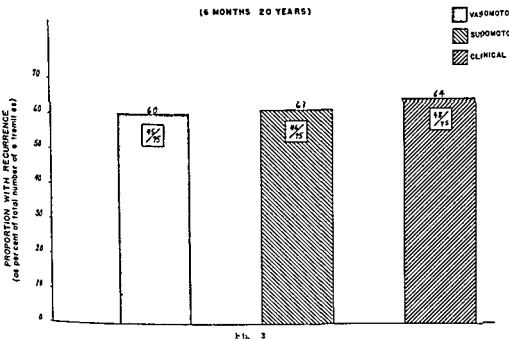


Fig. 3

Only 36 per cent of the 75 extremities were clinically cured. An additional 25 per cent were clinically improved while 36 per cent were not improved.

The data presented in Fig 1 are all inclusive for a follow up period of six months to twenty years after operation. Fig 2 illustrates the importance of the length of follow up in my evaluation of clinical results. Until 2 years the effectiveness of sympathectomy appears good. Beyond this critical time however, the results of sympathectomy become worse.

2 Relationship Between Clinical Recurrence and Demonstrable Return of Vasomotor and Sudomotor Activity—Fig 3 indicates that the incidence of recurrence of vasomotor and sudomotor activity are nearly identical. While

CLINICAL RESULTS AFTER SYMPATHECTOMY FOR RAYNAUD'S DISEASE OF THE UPPER EXTREMITY (6 MONTHS - 20 YEARS)

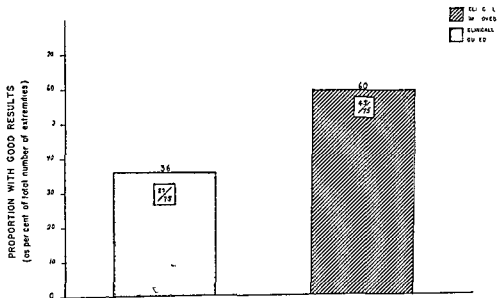
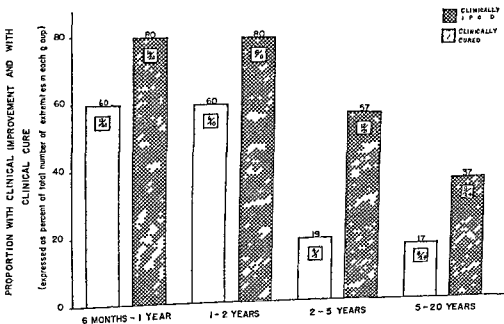


Fig 1

CLINICAL RESULTS OF SYMPATHECTOMY FOR RAYNAUD'S DISEASE OF THE UPPER EXTREMITY ACCORDING TO TIME AFTER OPERATION



Fig

tients and the clinical results were evaluated. These data are presented in Fig. 1. The category "Clinically Cured" represents those extremities in which attacks of vasospasm had not occurred after operation and could not be precipitated in the laboratory upon exposure to cold. The category "Clinically Improved" includes those extremities in which attacks of vasospasm did occur after sympathectomy, but the patients stated at the time of examination that they were better than they had been before sympathectomy. Individuals who stated that they were improved temporarily by operation but were not any better than before operation at the time of the examination were not included in the category of "Clinically Improved."

RESULTS OF SYMPATHECTOMY IN RAYNAUD'S DISEASE OF THE UPPER EXTREMITY

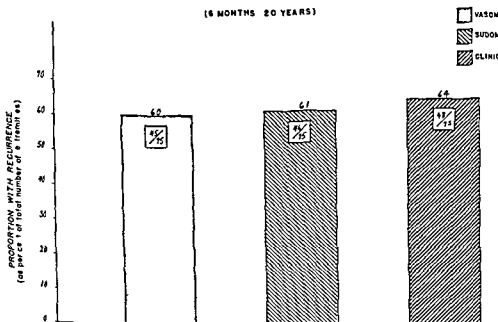


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2. *Relationship Between Clinical Recurrence and Demonstrable Return of Vasomotor and Sudomotor Activity*—Fig. 3 indicates that the incidence of recurrence of vasomotor and sudomotor activity are nearly identical. While

of the same order of magnitude, the incidence of clinical recurrence (64 per cent) is somewhat greater than the demonstrable recurrence of vasomotor and sudomotor activity. In other words, there are patients who continue to have clinical attacks of vasospasm even when it is not possible to demonstrate vasomotor and sudomotor nerve activity. This might be due to the vasospasm being a direct local phenomenon¹⁹ or to inability in a small number of instances to demonstrate vasomotor nerves by available techniques.

SUDOMOTOR AND VASOMOTOR ACTIVITY AND CLINICAL VASOSPASM IN THE UPPER EXTREMITY IN RELATION TO TIME AFTER SYMPATHECTOMY FOR RAYNAUD'S DISEASE

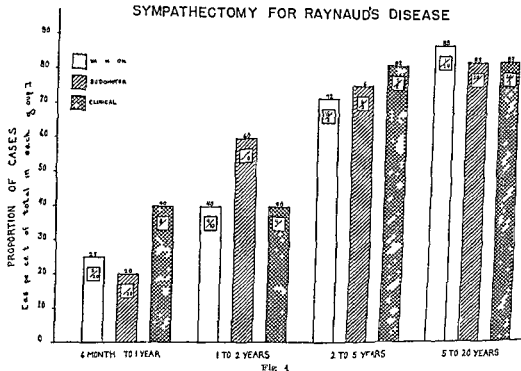


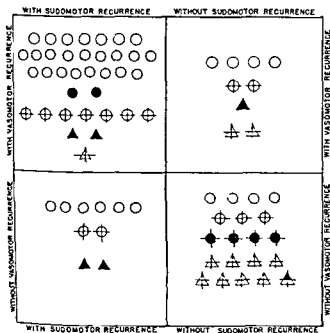
Fig. 4

Fig. 4 demonstrates that clinical, vasomotor, and sudomotor recurrences increase with time after operation. Furthermore, with the exception of sudomotor activity, there is a sharp increase in the rate of recurrence after 2 years from the time of sympathectomy. These data suggest that, whatever the causes for failure may be, they take time to develop and most of the development has already occurred by the end of the fifth year.

3. *The Influence of Type of Sympathectomy Upon the Results of Operation for Raynaud's Disease of the Upper Extremity*—A number of different operations have been done in this hospital for Raynaud's disease of the upper extremity. For purposes of this report three characteristics of these operations have been thought to be significant. These are (a) whether or not the denerva-

tion consisted of removal of the ganglion (b) whether C_8 and T_1 were included or excluded in the procedures and (c) whether spinal nerve roots of T_1 and T_2 were cut or left intact. Ganglionectomies below T_1 were all classed together regardless of extent since it is believed, from the anatomic standpoint that the extent of ganglionectomy below T_1 is not a variable of major importance.

CORRELATION OF LABORATORY FINDINGS WITH DIFFERENT TYPES OF SYMPATHECTOMIES FOR RAYNAUD'S DISEASE OF THE UPPER EXTREMITY



closed ganglionectomy
open preganglionic denervation
 Δ operation including C_8 and/or T_1
 \bigcirc operation not including C_8 and/or T_1
crossed spinal nerve roots 2, 3 interrupted intradurally
uncrossed spinal nerve roots 2, 3 secured (site uncertain) or left intact
 \triangle same as \triangle but with T_2 ganglionectomy

Fig.

(a) *Preganglionic section versus ganglionectomy* In Fig. 5 are represented all of the upper extremities studied with a different symbol for each of the operative variables described here. It appears that, regardless of the other variables, the proportion which showed no laboratory evidence of vasomotor and sudomotor recurrence was greater among those treated by ganglionectomy than among those treated by preganglionic sympathectomy. When type of sympathectomy was correlated with the clinical result, a similar relationship was found to exist (Table III).

(b) *Results related to the treatment of the stellate ganglion (C_8 and T_1) in the operation* Of the 17 extremities for which either the rami to the stellate ganglion were sectioned or the stellate ganglion was removed as a part of the operation, 47 per cent had sudomotor or vasomotor recurrence and a comparable

TABLE III RESULTS OF SYMPATHECTOMY OF THE UPPER EXTREMITY FOR RAYNAUD'S DISEASE ACCORDING TO THE TYPE OF SURGERY (FOLLOW UP 6 MONTHS TO 20 YEARS)

		SYMPATHECTOMY	CLINICAL
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†B Ganglionectomy of second and third thoracic sympathetic ganglia or lower with first thoracic sympathetic ganglion decentralized or resected without regard to the treatment of the second and third thoracic spinal nerve roots

†C Ganglionectomy below the first thoracic without regard to the treatment of the second and third thoracic spinal nerve roots

number had return of clinical vasospasm (Table IV, Fig 5). Without further qualification these data suggest that the results of sympathectomy are better when the stellate ganglion is included in the operation.

(c) *Results related to the treatment of the second and third spinal nerve roots in the operation.* Fig 6 shows that regardless of what else was done the recurrence rate was least in the group in which the inferior roots of T₂ and T₃ were interrupted intradurally. In the treatment of 7 extremities these spinal nerves were deliberately left intact. All 7 had clinical recurrence. At objective examination within 2 years, 5 of these had already recurred. By history, all had recurred within the first year. An analysis of recurrence using vasomotor recurrence as the index was made with reference to the treatment of the second and third spinal nerve roots and duration of follow up in Fig 6. From this it is apparent that in the early (6 months to 2 years) follow up period a higher percentage of recurrence has taken place in the intact or severed site unknown group as compared with those in which the nerve roots were known to be interrupted intradurally. Beyond the 2 year follow up period the recurrence rate in the two groups is about the same. The much lower recurrence rate in the group who had known intradural section suggests that this procedure while not necessarily preventing recurrence makes it possible only through slower or more difficult mechanisms.

TABLE IV RESULTS OF SYMPATHECTOMY FOR RAYNAUD'S DISEASE OF THE UPPER EXTREMITY RELATED TO THE TREATMENT OF THE STELLATE GANGLION (C AND T) IN THE OPERATION

TYPE OF PROCEDURE	EXTREMITIES	THOSE WITH RECURRENCE			
		VASOMOTOR OR SYMPATHECTOMY		CLINICAL VASOSPASM	
		NO	PER CENT	NO	PER CENT
Stellate Ganglion Intact	54	41	81	39	67
Stellate Ganglion Treated	11	4	41	9	55
(1) Decentralized	1	3		3	
(2) T ₁ Excised	4	4		3	
(3) C and T ₁ excised	1	1		1	
Totals	65	55	83	48	64

Lower Extremities

Results of Operation for Haynaud's Disease of the Lower Extremity Related to Extent of Sympathectomy—A clinical evaluation was made of 18 patients after lumbar sympathectomy. In 3 of these the laboratory studies were unsatisfactory so that objective laboratory data have been correlated in 15 of the patients or 30 extremities. Unlike the results of sympathectomy in the upper extremity which showed a high incidence of recurrence (Fig 3 Table III) results after lumbar sympathectomy for disease of the lower extremity

VASOMOTOR RECURRENCE AFTER SYMPATHECTOMY ACCORDING TO
TREATMENT OF THE SECOND AND THIRD SPINAL NERVE ROOT
AND DURATION OF FOLLOW-UP

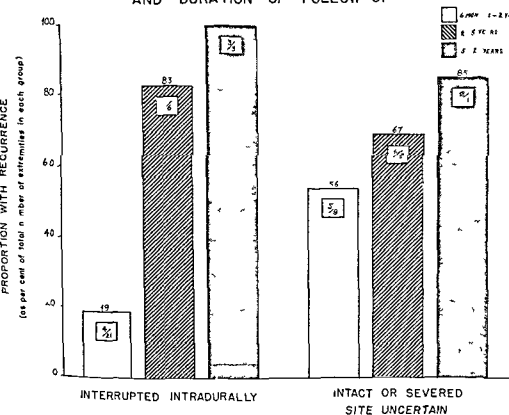


FIG 6

have been much more favorable (Fig 7). Furthermore the data indicate that the most satisfactory results were obtained with the most extensive ganglionectomies (Fig 7 squares, circles, and diamonds). Twenty-one or 70 per cent of the 30 extremities show a clinical cure in contrast to 36 per cent for the upper extremities (Fig 7 open symbols and Fig 8). It is also noteworthy that 13 of the 30 extremities examined showed either vasomotor or sudomotor activity or both, regardless of lack of clinical recurrence which was present in only 4 of the 13 (Fig 7). In the lower extremity as in the upper extremity it

is unwarranted to speak of permanent sudomotor and vasomotor paralysis merely on the basis that clinical recurrence has not taken place

UP-TOWARD EFFECTS OF SYMPATHETIC DENERVATION

Among the complaints of patients who have had sympathetic denervation of the extremities, 3 were prominent, namely exceptional dryness of the sympathectomized extremities, excessive perspiration about the trunk and thighs and an excessive tendency toward shivering with even slight lowering of the environmental temperature (Fig 9)

RECURRENCE OF CLINICAL VASOSPASM VASOMOTOR AND SUDOMOTOR ACTIVITY AFTER LUMBAR GANGLIONECTOMY FOR RAYNAUDS DISEASE

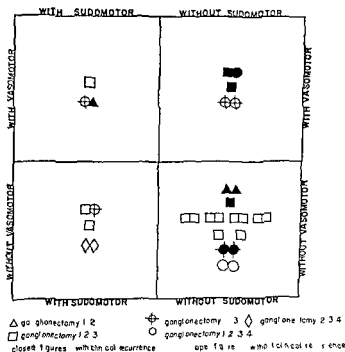


Fig 7

Excessive Dryness—The symptom of excessive dryness was taken as an untoward effect when the patient found it troublesome and could not control it by the use of ointments or creams. Among the entire group of 40 patients 20 (50 per cent) had this complaint. After sympathetic denervation of the upper extremities alone 10 out of 22 (46 per cent) complained of excessive dryness of the skin (Fig 10). Among the patients who had both dorsal and lumbar sympathectomies, however, 9 out of 16 (56 per cent) (Fig 11) presented this complaint. This suggests that the degree of annoyance from excessive dryness of the skin varies in proportion to the surface area denervated

Excessive Perspiration—The symptom of excessive perspiration was considered as an untoward effect where it caused the patient embarrassment or discomfort from wetting the clothing of the trunk and thighs through and through. Twenty-four out of 40 patients (60 per cent) had this complaint (Fig 9). When the group of patients who had dorsal sympathectomy alone are considered 13 of the 22 (59 per cent) had the complaint (Fig 10). Sixteen patients had both lumbar and dorsal sympathectomies and of these 11 or 69 per cent, complained of hyperhidrosis (Fig 11). Again the incidence of this complaint varies in proportion with the extent of sympathectomy.

RESULTS OF LUMBAR GANGLIONECTOMY IN RAYNAUD'S DISEASE OF THE LOWER EXTREMITY (1 to 20 years)

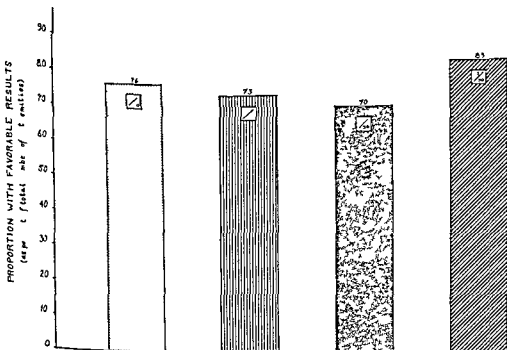


Fig 9

Shivering—The complaint of shivering was recorded only when the patients volunteered it. Their chief trouble was with uncontrollable shivering in air conditioned places such as theaters and stores. It happens that when the patient did not volunteer it and direct questions were then asked the complaint could not be elicited. Of the entire group of 40 patients 14 (35 per cent) had this complaint (Fig 9). Six of the 22 who had dorsal sympathectomy alone (27 per cent) complained of uncontrollable shivering (Fig 10). Of the 16 patients who had both dorsal and lumbar sympathectomy 8 (50 per cent) vol-

UNTOWARD EFFECTS AFTER SYMPATHECTOMY FOR RAYNAUD'S DISEASE



Fig 9

UNTOWARD EFFECTS AFTER DORSAL SYMPATHECTOMY FOR RAYNAUD'S DISEASE

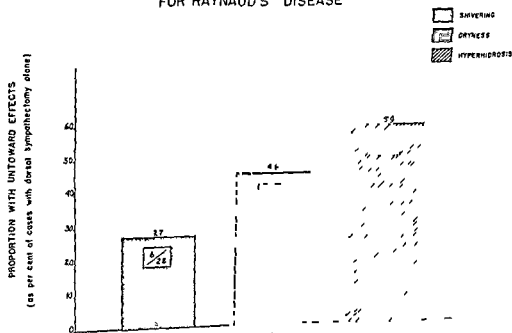


Fig 10

unleashed the complaint (Fig. 11). This disturbance is again proportional to the degree of sympathetic denervation and is attributable to a probable disturbance in the normal heat regulating mechanism. This is a well known phenomenon in sympathetomized animals.¹¹

It is important to emphasize that the data concerning the incidence of untoward effects refer to the patient as a whole and not to individual extremities as was the case in the compilation of data for clinical sudomotor and vasomotor recurrences. For example, an individual might complain of hyperhidrosis while showing evidence of varying degrees of vasomotor activity in an extremity.

UNTOWARD EFFECTS AFTER DORSAL AND LUMBAR SYMPATHECTOMY FOR RAYNAUD'S DISEASE

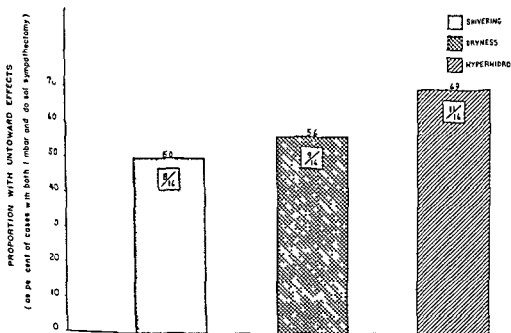


Fig. 11

DISCUSSION

The fundamental problem in the surgical management in Raynaud's disease and Raynaud's phenomenon has been that of recurrence of signs and symptoms after sympathectomy. While general agreement is to the causes of these recurrences is lacking, several possibilities present themselves. The first of these is the question of anatomic variation in the distribution of autonomic fibers to the upper extremity. The preganglionic elements of this innervation emerge from the anterior roots of the first to the tenth thoracic spinal levels¹⁷ (Fig. 12). Several investigators have suggested that T₁ is the upper limit for the preganglionic outflow to the upper extremity.¹² A further complicating feature

SCHEMA OF THE DISTRIBUTION OF SYMPATHETIC FIBERS TO THE UPPER EXTREMITIES

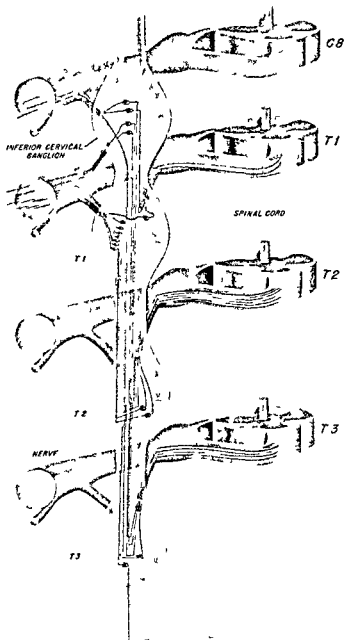


Fig 1

of the anatomy of this region is the occasional contribution to the brachial plexus of fibers in small branches from T_1 and T_2 .¹⁶ Anatomic variations such as this could explain some of the recurrences. It is generally conceded that the immediate results of sympathectomy for vasospasm in the upper extremity are excellent. Indeed, these excellent immediate postoperative results have been taken to indicate complete denervation of the upper extremity by decentralization of T_2 and T_3 ganglia alone. It should be noted that the vasoconstrictor action of only a few residual fibers might be masked by the vasodilator effect of ablation of the majority of fibers. Subsequent return of demonstrable vasoconstrictor activity could then be attributed to development of greater sensitivity in the partially denervated neurones and effectors.²⁵ However this mechanism should develop in a matter of 2 to 3 weeks. Figs 2 and 4 demonstrate that a large number of the recurrences occur after 2 years. Therefore it is not possible to explain these recurrences on this basis alone.

It has been suggested that regeneration of preganglionic fibers can account for the return of vasospasm after sympathectomy for Raynaud's disease.^{29, 30} The fact that autonomic nerve fibers regenerate with extraordinary ease in animals⁷ lends credence to this point of view. It is noteworthy that Simmons and Sheehan⁸ reported a decrease in adrenaline sensitivity in the digital vessels as clinical recurrences became manifest. This is an added indication that regeneration goes hand in hand with clinical recurrence.²

Figs 2 and 4 indicate that most recurrences take place by the end of the fifth year after operation. Beyond this time there is no appreciable increase in the number of recurrences. Since recurrence before the end of 6 months appears to be rare and is still not common before two years (Figs 2 and 4), it is reasonable to suggest that regeneration of sympathetic fibers accounts for most of the recurrences.

Increased sensitivity of smooth muscle after denervation has been thought to explain the recurrence of clinical vasospasm after ganglionectomy.³⁰ It is for this reason that independently, Telford³¹ (1935) and Smithwick³¹ (1936) devised a surgical approach which permitted a largely preganglionic denervation of the upper extremity. While there is adequate evidence from animal experiments that the acquisition of increased sensitivity by denervated structures is the rule,⁶ this phenomenon does not appear to play an important role in the surgical management of Raynaud's disease. In the first place since maximal sensitization occurs by the end of the second week after denervation¹⁴ one would expect recurrences to take place after a matter of weeks rather than months. The data presented in this report and corroborated by the observations of others,^{15, 29, 33} indicate that recurrence is rare or does not occur within such an early period. Furthermore the patient with clinical recurrence of vasospasm is rare in whom vasomotor activity cannot be demonstrated by blocking the peripheral nerves with procaine. For these reasons it is concluded that while sensitization of digital vessels following denervation probably does occur in man it certainly does not play a major role in the recurrences of clinical vasospasm following sympathectomy for Raynaud's disease.

Geoghegan and Alder³¹ (1942) have suggested that a reorganization of autonomic neurones takes place after severing the preganglionic nerve fibers

to the upper extremity within the dura, so that autonomic fibers which previously had no demonstrable motor effects in the arm developed the capacity to excite postganglionic neurones to the arm after the severance. The nature of this "reorganization" is not clear. Gehegan and Alder suggested that previously absent collaterals develop in the ganglionic cell stations from the intact preganglionic fibers passing through the ganglion. While such reorganization is a possibility, its mechanism has not been demonstrated. It is equally reasonable to assume, for instance that connections between the intact pre

RECURRENCES AFTER SYMPATHECTOMY FOR RAYNAUD'S DISEASE OF THE UPPER EXTREMITIES ACCORDING TO TREATMENT OF THE SECOND AND THIRD SPINAL NERVE ROOTS

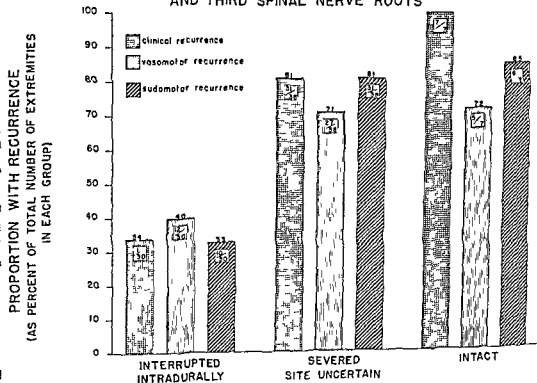


Fig. 13

ganglionic fibers and the postganglionic cells existed all the time but were not demonstrable until the partial preganglionic denervation of those cells had rendered them more sensitive to nerve impulses than they normally are.

The data presented here suggest that recurrences following sympathectomy for Raynaud's disease are due either to incomplete denervation or to regeneration of preganglionic nerve fibers. When denervation of the upper extremity is done according to classical anatomic concepts, the likelihood exists that in a small number of patients residual neurones exist, still connected with the

central nervous system^{16 17 20} The existence of these fibers and the development of functional capacity in them could explain some of the recurrences which take place in less than one year (Figs 2 and 4) Accepting this as explanation for some of the early recurrences it is reasonable to conclude that the remainder of the recurrences can be explained on the basis of regeneration of preganglionic fibers The ideal operation for Raynaud's disease, therefore is one which is complete and minimizes the chances for regeneration Complete decentralization of the postganglionic neurones to the arm and even ganglionectomy from T₁ down do not prevent recurrence (Fig 5 solid triangles) Recurrence in such cases can be attributed to the regeneration of preganglionic fibers to postganglionic cell stations in C₈ or in middle cervical ganglion In order to minimize the possibility for such regeneration Smithwick² (1940) developed a technique for intraspinal section of the anterior roots of T₁ and T₂ often resulting in an actual evulsion of the roots through the dura from the spinal cord Fig 13 shows a clear cut difference between the recurrence rate among patients for whom intraspinal severance of anterior roots was known to have been done and those for whom the roots were left intact or severed at an uncertain site probably extradurally Recurrences do occur in these cases but they are probably due to residual intact fibers and/or regeneration from sources other than T₁ and T₂ These sources could be fibers ascending the ganglionated trunk interrupted above T₄ As a matter of fact when recurrence occurs after intraspinal section, it is generally delayed (Fig 6) Since the sensitization effects of postganglionic denervation are thought not to play an important role in the recurrences, it would be reasonable then to combine intraspinal section with ganglionectomy in order to reduce further the likelihood of regeneration From the data in this report it will be seen that the best results have been obtained in patients for whom intraspinal section was combined with ganglionectomy (Fig 3) It is noteworthy however that the longest follow up in this group of cases is 15 years Final judgment must be reserved until a longer period of observation has been possible

In contrast to the results of sympathectomy for Raynaud's disease of the upper extremity the results of sympathectomy in the lower extremity have been good Of 30 extremities for which lumbar sympathectomy was done 21 (70 per cent) showed no clinical recurrence of vasospasm (open figures Fig 7) as compared with 27 out of 75 (36 per cent) in the upper extremity (Fig 1) An analysis of the objective vasomotor and sudomotor recurrences in the lower extremity after sympathectomy confirms that the results are better in the lower extremity than in the upper extremity Only 3 out of 30 extremities (10 per cent) showed evidence of both vasomotor and sudomotor activity while 17 of the 30 extremities (57 per cent) showed recurrence of neither (Fig 7) This contrasts with 48 per cent and 27 per cent for the upper extremity respectively (Fig 5) One explanation for the better results after sympathectomy for Raynaud's disease of the lower extremity than of the upper extremity has been that the sensitization to adrenalin following postganglionic section is avoided As discussed in the case of the upper extremity it is unlikely that the avoidance of such sensitization plays an important part in the difference in results

It is more likely that the better results for the lower extremity are due to the excision of longer segments of the ganglionated chain which makes regeneration more difficult. Thus extremities in which long segments of the chain were removed (open circles, squares and diamonds Fig 7) appear to have had a better result than those in which short segments were removed (triangles and crossed circles Fig 7).

SUMMARY AND CONCLUSIONS

1 This report comprises a clinical and laboratory study of 40 patients with Raynaud's disease or Raynaud's phenomenon. Thirty eight of these had sympathetic denervations of the upper extremities bilaterally except 1 (total of 75 extremities).

2 When studied 6 months to 20 years after operation, clinical recurrence was noted in 64 per cent (Fig 3), laboratory evidence of vasomotor activity was noted in 60 per cent of sudomotor activity in 61 per cent and of both vasomotor and sudomotor activity in 48 per cent of the 75 upper extremities.

3 Clinical and laboratory recurrences parallel each other and in the great majority of cases have occurred by the end of 5 years (Figs 2 and 4).

4 The results after sympathetic denervation for Raynaud's phenomenon of the lower extremity are better than the results after operations for disease in the upper extremities. Clinical recurrence was observed in 25 per cent of 36 lower extremities after operation. Laboratory evidence of both sudomotor and vasomotor recurrence was found in only 3 out of 30 extremities tested (Fig 7).

5 While sensitization may occur in man following postganglionic denervation it has not played an important role among the patients studied.

6 Residual autonomic pathways on the basis of anatomic variants could account for the very few early recurrences.

7 The evidence presented here for both upper and lower extremities indicates that recurrences are associated with demonstrably active vasomotor nerve fibers and that this activation is on the basis of regeneration of preganglionic axones.

8 In general the ideal operation is one which will completely denervate the extremity and at the same time prevent regeneration. The chances for regeneration are minimized by appropriate ganglionectomy and by intraspinal section of the preganglionic innervations.

REFERENCES

- 1 Adson, A. W. Surgical Relief of Raynaud's Disease. *Ann. Clin. Med.* 5: 161-166.
- 2 Adson.
- 3 Adson.
- 4 Adson.
- 5 Cannon, W. B. *Proc. Roy. Soc. Lond.* 1912, p. 312.
- 6 Cannon, W. B. A Law of Denervation. *Am. J. M. Sc.* 1918, 37: 750-1939.

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REFERENCES

- 1 Adson A W. Surgical Relief of Raynaud's Disease. Ann Clin Med. 5: 161 1911.
- 2 Adson
- 3 Adson
- 4 Adson
- 5 Cannon
- 6 Cannon W B. Inc p 312. A Law of Denervation. Am J M Sc 198: 731, 1910 1939.

- Collier, F. A., Campbell, K. N., Berry, R. L., Sutler, M. R., Lyons, R. H., and Moe G. K. Tetraethylammonium as an Adjuvant in the Treatment of Peripheral Vascular Disease and Other Painful States, *Ann Surg* 125 729-733 1947
- 8 Davis L., and Kanavel, A. B. Sympathectomy in Raynaud's Disease Erythromelalgia and Other Vascular Diseases of the Extremities, *Surg, Gynec & Obst* 42 1947
- 9 f Unilateral Cervical and Lumbar With Observations on Tonus, *Ann the Nervous System* ed 2, London, 1947
- 10
- 11 Geobegian, W. A., and Aidar, O. J. Functional Reorganization After Preganglionicectomy, *Proc Roy Soc Med* 50 315-369 1942
- 12 Goetz R. M. & Obst
- 13 Grimsom, K. Priscot tension and Circulation in Patients *Ann Surg* 127 968-991 1948
- 14 Hampel, C. W. The Effect of Denervation on the Sensitivity to Adrenine of the Smooth Muscle in the Nictitating Membrane of the Cat, *Am J Physiol* 111 611-621 1935
- 15 Kinmonth, J. B. Personal communication 1949
- 16 Karpis M. S. and Kuntz A. Inconstant Sympathetic Neural Pathways Their Relation to Sympathetic Denervation of Upper Extremity, *Arch Surg* 44 95-102, 1942
- 17 Kuntz, A. Alexander W. F., and Furcolo C. L. Complete Sympathetic Denervation of Upper Extremity *Ann Surg* 107 2, 31 1938
- 18 Lewis T. Experiments Relating to the Peripheral Mechanism Involved in Spasmodic Arrest of the Circulation in the Fingers A Variety of Raynaud's Disease, *Heart* 15 7 101 1929
- 19 Livingston W. K. Clinical Aspects of Visceral Neurology Springfield Ill 1935 Charles C Thomas Publisher
- 20 McDonough F. K. Homeostasis in the Sympathectomized Dog *Am J Physiol* 125 500-546 1939
- 21 Maes J. P. and Simeone F. A. Physiological Study of Regeneration of Splanchnic Paravertebral Distribution of by Stimulation er or Dermo meter' on Peripheral Nerve Injuries, Sympathectomies and Paravertebral Blocks *J Neurosurg* 3 181-191 1946
- 22 Royle N. D. The Treatment of Spastic Paralysis by Sympathetic Ramisection, *Surg, Gynec & Obst* 39 701-720 1924
- 23 Royle N. D. Sympathetic Trunk Section New Operation *M J Australia* 2 436 439 1928
- 24 Simeone F. A. Effect of Regeneration of Nerve Supply on Sensitivity of Denervated Nictitating Membrane to Adrenine *Am J Physiol* 120 466-474 1937
- 25 Simeone F. A. Cannon W. B. and Rosenblueth A. Sensitization of Superior Cervical Ganglia to Nerve Impulses by Partial Denervation, *Am J Physiol* 122 94-100 1938
- 26 Simmons H. T. and Sheehan D. Causes of Relapse Following Sympathectomy of the Arm *Brit J Surg* 27 243-250 1939
- 27 Skoog T. Ganglia in the Communicating Rami of the Cervical Sympathetic Trunk
- 28 Smitt Spasm (Raynaud's
- 29 Smitt rg Sympathetic De in *Surg* 112 1053 1100 1940
- 30 Telford E. D. The Technique of Sympathectomy *Brit J Surg* 23 448-450 1935
- 31 Telford E. D. The Results of Sympathectomy in Chronic Vascular Disease, *Proc Roy Soc Med* 37 621 1944
- 32 White J. C. and Hamlin H. New Uses of Tantalum in Nerve Suture Control of Neuroma Formation, and Prevention of Regeneration After Thoracic Sympathectomy *J Neurosurg* 2 402-413 1945
- 33 White, J. C. and Smithwick R. H. The Autonomic Nervous System New York 1941 The Macmillan Company

DISCUSSION

DR REGINALD SMITHWICK.—I should like to congratulate the authors of this paper on their careful and detailed study of this problem. I think their conclusions correspond with those of previous authors who have carried out similar follow up studies. The main problem is to produce a complete and permanent denervation of the upper extremity. Successful denervation of the lower extremity is much less of a problem.

There are a number of reasons why this is so. First as has been pointed out it may be impossible to denervate completely the upper extremity in an occasional patient. There are no accurate statistics on this point but occasional patients do have an outflow through the sympathetic trunk.

Secondly, even in the peripheral nerves themselves, it is possible for fibers to get to both the arm and the leg without ever passing through the ganglionated chain. Consequently ganglionectomy, no matter how extensive may not interrupt all impulses to an extremity. Ireganglionic section theoretically would but in the case of the arm, it is not possible to divide the anterior root of the first thoracic nerve because of the motor weakness which would ensue.

In addition there are other differences between the upper and lower extremities which make the problem more difficult in the case of the former. In general the sympathetic control of the blood vessels of the upper extremity is less active than of the lower extremity. Also a local fault in the blood vessel, which renders them more sensitive to cold, is more common in the upper extremity. Scleroderma is much more likely to involve the upper extremities. This detracts from the late results.

The major problem, however, is to prevent regeneration of the vasoconstrictor fibers. Ganglionectomy will not do this because the distance which separates the upper thoracic segments from the tracheal plexus is very short. Preganglionic section, theoretically, should prevent regeneration. Actually it is the most effective safeguard against regeneration which has as yet been devised. It must however be performed in a certain manner. The anterior roots of the second and third and preferably of the fourth thoracic nerves as well, must be sectioned intrinsically. Rhizotomy and extraspinal root section will not suffice. This is best accomplished by resecting the inner portions of the third and fourth ribs which gives excellent exposure. The arachnoid is gently separated from the anterior roots after dividing the posterior roots proximal to their ganglia in order to expose the anterior roots. The anterior roots are then divided with scissors, removing 1 cm. or so of their intraspinal portions. They are not avulsed. This term should not be used as it implies the use of force which is dangerous. Whether one then removes the decentralized ganglia or simply encases them in a silk cylinder is of secondary importance. Removal of the first thoracic or inferior cervical ganglia should be avoided in unilateral procedures because a Horner's sign will result. Regardless of this removal of these ganglia will not prevent regeneration.

In reporting results it is essential that patients be divided into groups according to the technique of operation. The best results in my experience as well as in that of others have been obtained when the upper extremity is denervated by intraspinal root section. This is the most important single factor affecting late results.

DR LINTON. I would like first to compliment Dr Felder and Dr Simone on doing such an excellent job on this follow up of Rhynaud's disease. I had very little to do with the actual follow up study and came into the problem chiefly from the fact that I operated upon a number of the patients. As I have observed patients with this disease over a good many years it is my opinion that our chief problem in the cure of the condition, especially in the upper extremities, lies in the fact that we have not developed an operation which will prevent recurrence of the vasospastic condition in the hands. It is my belief that one of the main reasons for this high rate of recurrence, as demonstrated by this follow up study is the fact that we have not done a radical enough operation.

It is generally agreed that the chief outflow to the upper extremity is through the second and third intercostal nerves via the second and third dorsal ganglia. There is no

question that the Smithwick type of operation, removing the second and third dorsal nerves and cutting the rami of the second and third dorsal ganglia, is a great improvement over the original stellate ganglionectomy. However in view of the fact that many of the patients with the Smithwick procedure have had recurrences I have attempted to do a more radical operation and to date it seems to give somewhat better results although it is still too early to draw any definite conclusions.

The actual outflow to the upper extremity in the human being has never been definitely ascertained but our follow up studies and the reoperation of patients who have had recurrences with the Smithwick procedure indicate that there is in a good many patients, an outflow through the first dorsal nerve directly to the first dorsal ganglion and possibly the inferior cervical ganglia. For that reason I believe that an operation to be effective for Raynaud's disease of the upper extremity must of necessity produce a Horner's syndrome. In order to attain this, in addition to doing the Smithwick type of procedure I have for the past few years removed dorsal ganglia 1, 2 and 3, and severed the rami of the inferior cervical ganglia enclosing them in a cotton cylinder with the hope that this might prevent regeneration. The patients in whom this has been done and in whom there were recurrences following the Smithwick procedure have had marked improvement.

In order to do this type of operation satisfactorily in patients previously operated upon necessitates a trans-thoracic approach removing the fourth or fifth rib. I believe the answer to the problem of Raynaud's disease will be obtained only by further careful follow up studies such as have been presented here today along with very accurate descriptions of the operative procedures of what was done.

HYPERTENSIVE VASCULAR DISEASE ASSOCIATED WITH QUADRILATRAL RAYNAUD'S DISEASE RELATED BY TOTAL SYMPATHECTOMY

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IT IS a curious fact that in a series of 500 conservative patients with essential hypertension subjected to thoracolumbar sympathectomy not one instance of Raynaud's disease was observed preoperatively. One of us (I. L.) then recommended total sympathectomy for two patients suffering primarily from Raynaud's disease of all four extremities associated with an essential hypertension. These patients sought medical advice primarily for indolent ulcerations of the tips of the fingers in one and of the great toe in the other and the hypertensive element was apparently of lesser importance to each of these individuals.

The etiology of Raynaud's disease has remained obscure in spite of intensive studies by many workers. Raynaud himself as well as the majority of students of this condition have ascribed the abnormality as related to an overactivity of the sympathetic nervous system. White and Smithwick¹ defined "Raynaud's disease as a form of peripheral vascular disturbance caused by tonic contraction of the smaller arteries of the extremities. They added that

keeping in mind all the facts which have been reviewed we believe that the greatest weight of evidence is against Lewis' theory that the local fault is primary and upholds Raynaud's original idea that at the onset of the disease the recurrent attacks of symmetrical vasospasm are due to an abnormal activity of the vasoconstrictor nerves. Any theory of the etiology of Raynaud's disease must be applicable to early as well as late cases and equally to the hands and feet." Adson and Brown² were of the opinion that in early Raynaud's disease the abnormality is wholly in the vasomotor nerves.

The view that the primary factor in Raynaud's disease lies in a fault in the digital arteries and that this fault is in the nature of an abnormal sensitivity of the artery to direct stimuli, particularly to relatively low temperature has been advanced by Lewis.³ He held that the vasomotor activity is normal but that the peripheral spasm is due to an increased susceptibility to cold on the part of the smooth muscles in the digital arterioles.

In spite of a variety of clinical experiments, no theory satisfactory to all investigators has been evolved. As a result of our observations of the two patients reported in this paper we are inclined to agree with Morton and Scott⁴ that both the local fault and an overactivity of the sympathetic nervous system must operate to produce the clinical picture of Raynaud's disease.

Perera⁵ has pointed out that hypertension is not a disease in itself, but rather a manifestation of hypertensive vascular disease, and that the latter assumes importance when damage occurs to the brain, eyes, heart and kidneys. Goldring and Chasis⁶ have stated that hypertension is the earliest clinically recognizable disturbance of this disease and that it results from the constriction of the peripheral arterioles, this constriction leading to an increase in the total effective peripheral resistance and hence to elevation of diastolic and systolic blood pressure. Further evidence that individuals suffering from essential hypertension have an overactive sympathetic nervous system has been supplied by Hines and Brown⁷ by means of the cold pressor test.

The role of sympathectomy in the treatment of essential hypertension is based on the principle that elimination or curtailment of the neurogenic factor would lead to relaxation of the arterioles of the splanchnic area and elsewhere, and hence lower the systolic and diastolic pressure, lessen the work of the heart and possibly improve renal blood flow. The evidence for improvement in renal blood flow following sympathectomy is meager and gross tests of renal function fail to show improvement. Hembecker⁸ has elaborated an interesting thesis that sympathectomy may lessen the output of the medullary part of the adrenal gland and thereby interfere with a vicious cycle which includes the adrenal glands, the kidneys, the frontal lobes and hypothalamus and the anterior and posterior parts of the pituitary gland.

Regardless of how it works, thoracolumbar sympathectomy of the Smithwick type⁹ or total sympathectomy of Grimson¹⁰ have profound influence on the blood pressure. Approximately one quarter of the patients operated upon for essential hypertension will obtain excellent results in a variety of ways, and another two quarters will obtain a moderate fall in blood pressure and some improvement in cardiac function and the eye grounds as well as relief of symptoms.

Surgical treatment with sympathectomy still remains the most satisfactory method of treatment in Raynaud's disease, stated Allen Barker and Hines. White and Smithwick¹ reported that in 9 patients with 18 involved lower extremities very good results were obtained from lumbar sympathectomy, whereas in 93 upper extremities with varying degree of local damage good results were obtained in 65 and 23 were improved. One of the serious difficulties with sympathectomy for Raynaud's disease, especially of the upper extremity, has been the attainment of a complete and lasting sympathetic denervation. White and Smithwick¹ have stated that surgical denervation must be complete or it will be of little value. Ray and Console¹¹ have studied thoroughly the problem of sympathetic denervation of the lower extremities and have found that inadequate removal or the extent of removal of the lumbar ganglia could not explain the persistence of sympathetic activity. Further, the factor of regeneration is not the answer to the evident return of sympathetic activity in certain areas of the lower extremities. They demonstrated that there are residual pathways having their origin in the thoracic 12 through lumbar 3 dermatomes after standard sympathectomies.

and may be interrupted by anterior rhizotomy spinal anesthesia, tetraethylammonium and procaine block or division of the lumbar nerves." Ray¹² believes that similar residual pathways will be demonstrated to the upper extremities which are not ablated by complete upper thoracic and inferior cervical sympathectomy, whatever its type.

From a therapeutic point of view, the two patients reported in this paper were treated by total sympathectomy the first one in four stages the second in two stages. Theoretically, it would seem like an ideal surgical procedure but as one of us (J. L.) has pointed out, there are several theoretical objections to this operation not the least is the one De Bakey and his associates¹⁴ presented in their report on the "borrowing lending" mechanism as an important hemodynamic factor. They stated that measures designed to produce dilatation of the entire vascular bed are of doubtful value in the treatment of arterial insufficiency to an extremity. They were concerned chiefly with drugs such as tetraethylammonium chloride but, in effect, the performance of a total sympathectomy is closely akin to the general vasodilating effects of certain drugs. The potential harm of such a procedure was evidenced by the early worsening of the lesions in the extremities of each patient before significant improvement was noted.

CASE REPORTS

CASE 3—A 26 year old white woman was first seen Dec. 3, 1946. Chief complaints were ulcers of the tips of the left third and right fourth fingers with discoloration, coldness and numbness of all of the fingers of both hands except the thumbs. The patient stated that she had been in good health until the winter of 1936 when she first noticed blueness and numbness of the finger tips on exposure to cold. In September, 1947 she developed ulcerations of the finger tips which failed to heal despite treatment with various antiseptic solutions and penicillin ointment. The patient stated that her feet also became cold and numb with peculiar mottling of the skin.

Past history revealed that she had had palpitations on climbing stairs for the past six months. Menstrual periods were regular but scanty in flow. She was not aware of any hypertension until September 1947 when she was so informed by a physician whom she had consulted because of the vasoconstrictive symptoms.

1. Ulcerations were present on tips of the right fourth and left third fingers. There were scars of healed ulcerations of several of the finger tips and about the nails. The toes were cyanotic and cool without any ulcerations. There was 1 plus pretibial edema of both legs. The skin showed a peculiar mottling with slight cyanosis. The peripheral arteries were easily palpable. Oscillometric readings were normal in all four extremities. Blood pressures were as follows: Lying left, 170/110 right 160/120 sitting, left, 170/110 standing, left 160/110, exercise left 210/100. Sodium Amytal test showed a decrease in blood pressure from an initial reading of 170/110 to 140/95. Blood chemistry: Blood urea nitrogen, 10.0, nonprotein nitrogen, 27.0 creatinine, 1.1 cholesterol, 160. Blood count: Red blood cells 4,900,000, hemoglobin 13.9 white blood cells 14,200 poly morphonuclears 68, lymphocytes 29, monocytes 3. Routine urine: specific gravity 1.016 protein, trace, bacteria frequent, epithelial cells few squamous amorphous sediment frequent phosphorus, crystals some triple phosphorus.

Urea clearance test 57 per cent of average normal the first hour, 43 per cent of average normal the second hour

Newburgh Concentration Test 8 AM specific gravity, 1.010 protein faint trace rare red blood cells 1 to 4 white blood cells frequent epithelial few bacteria 10 AM specific gravity, 1.014 protein, faint trace, occasional white blood cells many phosphates, occasional epithelial 12 AM specific gravity 1.020 protein faint trace occasional white blood cells many phosphates frequent calcium phosphates

Eye grounds Fundi showed venous engorgement, spasm of the arteries arteriovenous nicking and in the right fundus at 9 o'clock there was a cotton wool exudate and a small recent hemorrhage Six foot heart plate Examination of the thorax showed a hypertensive aortic type heart There was moderate left ventricular preponderance with the relatively more deviation at the left exceeding that to the right suggesting probable left ventricular enlargement There was also an accentuation of the aortic arch Except for a slight thickening, the peripheral lung fields were clear Electrocardiogram revealed pattern consistent with left ventricular hypertrophy

It was decided that the patient should first have a thoracic sympathectomy to relieve the peripheral gangrene in the upper extremities Accordingly on Dec 16, 1947 a right thoracic sympathectomy was performed There was difficulty in visualizing the stellate ganglion and consequently it was not removed The patient made an uneventful recovery and on Dec. 22 1947 a left thoracic sympathectomy was performed The stellate ganglion was removed

The pathologic diagnosis of the surgical specimens in both procedures was sympathetic ganglia and nerves

The patient again had an uneventful postoperative course and was discharged in good condition on Jan. 4 1948 The mottling of the skin and the ulcerations were still present The blood pressure in the left arm was Lying 200/100, sitting, 190/110 standing 150/100

The fingers of both hands became only slightly warmer and were still cyanotic In fact within the first forty eight hours after each operation they appeared to be slightly worse However at the end of one week some definite improvement was noted which continued

Within the next month on a 1000 calorie diet the patient's weight decreased from 169 to 150 pounds and she felt well The blood pressure fluctuated between 190/120 and 160/106 in the left arm The finger tips healed slowly but completely The fingers were still cold but improved There was some blueness in the left third finger and the right fourth finger The perceptive sense which was reduced postoperatively returned to both hands completely by the end of the month The blood pressure was little affected by the thoracic sympathectomy so that on Feb 3 1948, the patient was readmitted for bilateral thoracolumbar sympathectomy

Her blood pressures were as follows Lying 196/120 sitting, 178/110 standing, 176/120 exercise 194/128 Urine The specific gravity was 1.023 There was a faint trace of protein Microscopic examination revealed occasional white blood cells few urates and frequent bacteria

Blood chemistry Urea nitrogen 8.0 mg per cent nonprotein nitrogen, 25.0 mg per cent

On Feb 6 1948 a left and six days later right thoracolumbar sympathectomies were performed

For the first week the blood pressure fluctuated between 90/60 and 110/80 At the end of the first week the blood pressure lying down was 120/80 sitting, 100/80 standing 90/40

Two months later the blood pressure readings were lying right, 120/70 sitting right, 126/84 left 114/70 standing right 90/50

The fingers were well healed and appeared normal in color and temperature

On Aug. 1 1948 six months following the last sympathectomy the patient stated that she felt completely well She had no more attacks and there were no color changes

in any extremity on exposure to cold water. As yet there had been no exposure to cold weather. She complained only of extreme perspiration over her back. The fingers were completely healed but the tips were a little cool. The blood pressures were lying right, 128/90, left, 122/84 sitting, right 128/80, left, 134/94, standing right, 140/96 left 114/10.

On Dec 21, 1948 the finger tips were still completely healed. The tips of the fingers became cyanotic only on exposure to cold weather and cold water (patient is a cook). Blood pressures were lying left, 140/90, right, 140/90, sitting left, 100/94 right, 100/96, standing left, 144/80, right, 126/90. The patient was again seen on May 12 1949 and at that time stated that she felt entirely well. The only abnormalities noted were slight sensitivity of the tip of the right fourth finger and that both hands perspired at times during the past two months. On exposure to cold during the past six months the fingers occasionally became cyanotic but there was no pain or numbness. The feet remained dry and were asymptomatic. Weight was 119 pounds and blood pressures were lying right, 168/98, sitting right 150/100, left 170/100 standing, right 168/100. Fig 1 shows a graph of the blood pressures.

TOTAL SYMPATHECTOMY

CASE 1 NO 28 YOF

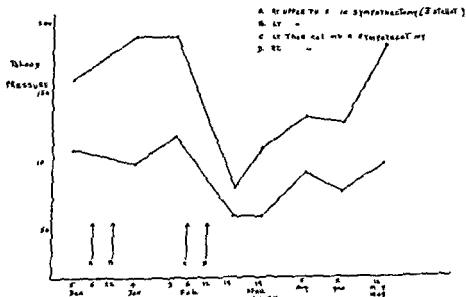


Fig 1 (Case 1) — Graph of the blood pressure of N O 8 year old woman following total sympathectomy

CASE 2 — 1 16 year old white woman had been suffering repeated attacks of pain numbness and coldness of the extremities whenever exposed to cold. This began with painful blanching in the left fifth finger eighteen years before which gradually involved the whole hand. The same symptoms began shortly in the right hand and were soon followed by the same syndrome in the toes of both feet. Each year the attacks occurred with greater frequency until there was no time she was completely free of the complaint even in the summer. She had an ulcer on the right index finger which took three years to heal.

In 1942 when giving blood to the Red Cross she learned that she had high blood pressure. In October 1944 this patient had an ingrown toenail excised. Following this

She developed an ulcer which failed to heal. This too became painful on walking over a few blocks. On the other hand pain sometimes came on at rest and was relieved by walking. Physical examination revealed the following. Fundus examination. In the right fundus there was marked arteriovenous nicking and arterial spasm. In the left was seen a classical corkscrew arteriole reaching into the macular area. There was tortuosity of the arterioles on both sides but no hemorrhage.

Lungs were normal. Heart showed regular sinus rhythm rate 100, no murmurs, sounds of good quality. Abdomen was obese. Liver, spleen and kidneys were not palpable.



Fig. 1 (Case 1)—A. Anterior view of the feet one week after the left total sympathectomy showing gangrenous ulceration of the left great toe. B. Lateral view.

All the extremities were cool. On the left first toe there was an open ulcer which covered most of the distal phalanx (Fig. 2, A and B). The peripheral arteries were palpable, oscillometric readings were normal. The skin temperature was markedly reduced in the left foot. On admission, the following laboratory examinations were noted. Roentgenogram of the chest revealed an aortic type heart without any gross enlargement. The electro-

cardiogram was abnormal but without any definite diagnostic pattern. The sedimentation rate was 41. Urine had a specific gravity of 1.010 with a faint trace of protein. Blood urea nitrogen was 10.5, glucose 60, hemoglobin 11.8 (m), red blood cells 4.6, white blood cells 12,100 with a normal differential.



Fig 3 (Case).—*A*, Anterior view of feet four months postoperatively showing the lesion of the great toe, left foot, to have healed. Note that the second toe, left, is in good condition at this time. *B*, Lateral view.

Amytal test showed a decrease in blood pressure from an initial 200/100 to 140/84. Blood chemistry: Urea nitrogen 9.5 mg per cent, nonprotein nitrogen 29.0 mg per cent, glucose, 50 mg per cent, vitamin C 0.60 mg per cent. Sedimentation rate was 40. Urea clearance test: 67 per cent of average normal the first hour, 63 per cent of average normal the second hour. Mosenthal test showed a decreased ability to concentrate the urine.

On April 20, 1948 a left total sympathectomy was performed. Immediately following the operation the left foot and leg appeared cool. This continued for about forty eight hours with only occasional intermittent improvement. About two days later there was some improvement of the left foot and leg as compared to the right. Soon however the left foot appeared cool and there was marked pain particularly in the left big toe. The toe appeared even more cyanotic than prior to the operation. The day before the second operation necrotic pustular blisters were noted on the tips of all of the toes of the left foot. On May 17, 1948, a complete right sympathectomy was performed in essentially the same manner as the left side.

The postoperative course was complicated by a superficial wound infection, the development of an abscess on the dorsum of the right wrist, and an abscess of the buttock. All of these cleared following incision and drainage but healing was much more prolonged than usual in spite of a normal level of plasma proteins and a high protein high vitamin intake.

TOTAL SYMPATHECTOMY

CASE 2 B.L. 48 yrs F

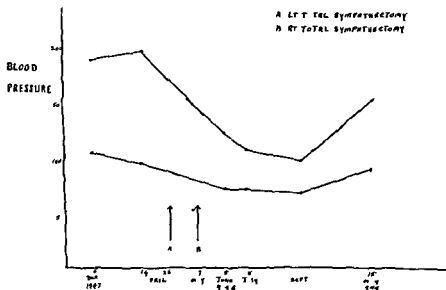


Fig 4 (Case) — Graph showing the blood pressure of B.L. 48 year old woman after total sympathectomy

Following the second operation the blood pressure ranged between 120/70 and 130/80. The ulcer was still present on the left big toe and appeared larger than before the operation. The tips of the other toes also appeared cool and cyanotic. The patient was discharged on the forty first day after the second operation.

Two months later all wounds were completely healed including the areas of peripheral gangrene on the toes of the left foot Fig 3 A and B. The skin temperature of the left foot was lower than the other three extremities. However the toes were pink and not at all cyanotic. There was a variable amount of soft tissue defect present on all the toes of the left foot. There was no pain nor was there any symptom referable to hypertension. There was no dyspnea on exertion. The blood pressures were: Lying, right 134/84 left 136/80 sitting right 92/66 left 89/62 standing right 4/00 left, 64/00.

The patient stated that she had not felt so well for many years although during the immediate postoperative period she had never been so miserable. She was examined

May 15, 1949 approximately one year postoperatively. In general she felt well, had no symptoms referable to the hypertension, and blood pressures were 140/90, right, 130/110 sitting, right, 160/90, standing right, 140/100.

The hands have remained dry and no new ulcers have formed. They have remained warm and pink at all times. The toes have also remained in excellent condition with the exception that for the past four months she has had a superficial ulcer 10 by 15 mm at the tip of the second toe. All toes are warm and pink and the pulsations are entirely normal. The feet have at no time required. Fig. 4 shows a graph of the blood pressures.

DISCUSSION

There are several points of interest brought out by the two cases described here. First, one patient has obtained satisfactory improvement from the viewpoint of her hypertensive vascular disease during the fifteen month postoperative period of observation, and has been markedly helped in regard to the Raynaud's disease of the fingers. This patient had an ablation of the stellate and second and third thoracic ganglia on one side and removal of only the second and third ganglia on the other side. Both hands are equally improved without further ulceration or pain, and both began to sweat approximately fifteen months postoperatively. The explanation of these changes may be on the basis of readjustment of residual pathways or may be ascribed to regeneration. The question of adrenergic sensitivity playing a role seems unlikely because on one side the procedure was postganglionic (stellate and thoracic two and three) whereas on the other side the stellate ganglion was not removed. There has been exactly similar improvement in each hand and a simultaneous return of sweating and cyanosis in each hand on exposure to cold. On the other hand the toes have remained pink and warm and have been symptom free.

The second patient has also had a satisfactory improvement in the hypertensive vascular disease, although recently the blood pressure has mounted toward the preoperative level. The fingers have remained healed, warm, pink, and dry for twelve months following ablation of the stellate ganglion bilaterally along with the entire sympathetic chain to below lumbar 3. This woman presented the unusual and unexpected finding of complete healing of the ulcerations of the toes following a period of postoperative relaxation only to have a new ulceration develop on the second toe of the left foot some eight months postoperatively, and this ulcer has resisted all forms of therapy which have been applied in the outpatient department. Up to the present the patient has refused to be readmitted to the hospital. The feet and toes are warm, dry, and pink, and the ulcerated toe appears entirely normal except for the superficial 10 by 15 mm defect at the tip. Clinically the lumbar aspect of the sympathectomy is complete and yet the local fault is sufficient to cause further ulceration. There is no evidence of any change in the palpable arteries of the feet.

Finally, the fact that there have been only 2 patients with Raynaud's disease in a series of 500 patients subjected to sympathectomy for hypertensive vascular disease would suggest that the two diseases are merely coincidental in the same patient, that one must invoke as an associated factor the local fault

aspect and that both conditions can be improved by total sympathectomy Ray¹ has observed 1 patient with the two diseases in his series of approximately 400 sympathectomies. He has seen 1 other individual who has not accepted the advice for surgical intervention and we have 2 more nonoperative patients with the two diseases. One was in chronic congestive heart failure and operation was not advised, whereas the other patient failed to return to the clinic following his initial work up.

SUMMARY

- 1 The incidence of the occurrence of Raynaud's disease and hypertensive vascular disease in the same patient is relatively infrequent.
- 2 The theories of etiology of Raynaud's disease and hypertensive vascular disease are discussed briefly and the role of surgery of the sympathetic nervous system in each disease is considered.
- 3 Two cases, both white women who were moderately improved by total sympathectomy, are reported.
- 4 The viewpoint that Raynaud's disease is probably the result of an interrelation and concomitant action of a local fault (hypersensitivity of the arterioles of the digit to a direct stimulant such as cold) and an overactivity of the sympathetic nervous system is upheld.

REFERENCES

- 1 White J C and Smithwick R H. The Autonomic Nervous System: Anatomy, Physiology and Surgical Application ed 2 New York 1941, The Macmillan Company 469 pp.
- 2 Adson A W and Brown G L. 157 in Allen E W, Barker N W, Hines E A. Peripheral Vascular Diseases Philadelphia 1946 W B Saunders Company.
- 3 Lewis T. Vascular Disorders of the Limbs New York, 1906 The Macmillan Company, 111 pp.
- 4 Morton J J and Scott W J M. Some Angio-vascular Syndromes in the Extremities Ann Surg 84 935-9 1911.
- 5 Ferrera A. Hypertension: A Manifestation of Hypertensive Vascular Disease New York State J Med 48 1724 1948.
- 6 Goldring W and Chalmers H. Hypertension and Hypertensive Disease, New York 1944 Commonwealth Fund p 2.
- 7 Hines F A Jr and Brown G E. A Standard Test for Measuring the Variability of Blood Pressure: Its Significance as an Index of the Prehypertensive State Ann Int Med 7 209-217 1933.
- 8 Heinbecker L. Factors Limiting Surgery for Essential Hypertension Ann Surg 126 333 1947.
- 9 Smithwick R H. A Technique for Sympathetic Resection for Hypertension, SURGERY 7 18 1940.
- 10 Grimsby K S. Total Thoracic and Partial to total Lumbar Sympathectomy and Celiac Ganglionectomy in the Treatment of Hypertension Ann Surg 114 753-767, 1942.
- 11 etic Pathways After Paravertebral
- 12 ated With Quadrilateral Raynaud's
- 13 The "Borrowing Lending" Hemo
- 14 d Its Therapeutic Application in
- 15 Peripheral Vascular Disturbances Ann Surg 126 6 1947.

UNUSUAL CASE OF GASTROINTESTINAL HEMORRHAGE

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CASE REPORT

A G was a white male aged 7 years. This small boy was admitted on Sept 28, 1946 with a history of having been run over by a football player while standing on the side lines watching a football game. He was immediately unconscious, and when he recovered, he complained of severe abdominal pain. On admission to the hospital shortly after the accident he was obviously in shock and showed evidence of intra abdominal bleeding. An emergency laparotomy was performed several hours after admission and a stellate laceration of the dome of the liver was found beginning at its base near the exit of the hepatic veins and extending across the dome close to the anterior edge of the liver with another extension near the center of this laceration giving it a 1 shaped appearance. The laceration appeared to be rather deep, although its exact depth was not determined. It was bleeding freely when first noted. Bleeding was controlled by compression of the portal vein and hepatic artery at the foramen of Winslow. The laceration was repaired and bleeding apparently controlled, using interrupted catgut sutures. Blood was replaced by transfusions. The patient responded well initially, and by Sept. 30, 1946 the red count was 4,000 with 17% Gm of hemoglobin. On Oct 7, 1946 he complained of upper abdominal pain and a blood count was done on Oct. 8, 1946, which showed a red count of 3,950,000 with 11 Gm of hemoglobin. He continued to have several episodes of severe crampy upper abdominal pain and each time he vomited. No blood was noted in the vomitus. The red count fell to 3,900,000 with 9 Gm. of hemoglobin on Oct 9, 1946 and it was necessary to give him a transfusion. The patient also looked somewhat pale. Re exploration was done on Oct 11, 1946 with the idea that he might have secondary hemorrhage from the liver but the suture line seemed intact and the surrounding liver felt somewhat soft on palpation. His course was rather stormy after the second operation and he continued to have episodes of abdominal pain which were associated with vomiting. He vomited first plain fluid and then a small quantity of bright red blood and shortly afterward had a large watery bowel movement. In addition he was exhibiting some evidence of infection as shown by temperature elevation. Chest x-ray examination showed fluid in the right side of the chest and an elevation of the diaphragm. It was established by means of aspiration that there was some subphrenic infection. This was treated by repeated aspiration and institution of penicillin and streptomycin. The subphrenic infection appeared to improve but his course was still quite rocky and several transfusions were necessary to keep the blood count relatively normal. Fever continued and on Nov 2, 1946 the abdomen was re explored and the subphrenic space was drained. This so called subphrenic abscess consisted mainly of blood clot which seemed to be completely and on culture no definite organisms were found.

Following the third operation the patient once more appeared improved but shortly afterward he began again to have episodes of severe epigastric pain referred through to the back, accompanied by eventual vomiting of small amounts of bright red blood and the subsequent passage of a large amount of digested blood by rectum. At this time the idea that the bleeding might be coming down the common duct was seriously considered. Several of these episodes were so severe as to be practically exanguinating and only because blood of blood were kept constantly near by for his use did he survive. Although he never had an obvious jaundice, on Dec 19, 1946 the icterus index was 20 and several other chemical tests within normal limits.

Since these episodes continued on Dec 31, 1946 exploration through the abdomen was once more done. No free blood was found. The stomach and duodenum were opened and inspected and no lesion could be seen. No blood could be expressed through the common duct. Vater. The gall bladder was aspirated and no blood could be obtained. The common duct was opened and profuse bright red blood flowed from it in spurts simultaneous with the

arterial pulse. This was controlled by compressing the duct. The patient had vomited blood for the second time during the day just two hours before this operation and, because of his very poor condition, a catheter was left in the common duct, and the wound was closed. We felt it unwise to open the right lobe of the liver although we suspected the source of the bleeding to be in the depths of the stellate laceration. Cholangiography was done on Jan. 8, 1947, and a markedly dilated common duct, which was thought to be filled with blood clot and some opaque bile pigment was seen. The patient was again prepared for operation, since the episodes were continuing, and on Jan. 16, 1947, thoracoabdominal exploration of the liver was carried out. Underlying the diaphragm, at the region of the original wound in the liver was a shallow channel extending up to the midline which contained a small amount of thin fluid and some necrotic material. This channel on further exploration, was found to extend deeply within the substance of the liver toward the hilus and here it was filled with organized blood clot. Deep within the substance of the liver there was a large cavity. This cavity was tightly filled with a large blood clot which was fairly well organized and rather firmly adherent to the posterior and superior walls. On the floor of this cavity near its lateral termination a small vessel was sutured and a rubber catheter was inserted. The thoracic wound was closed. This procedure was

also only temporary and on Jan. 22, 1947, the wound was reopened, the cellulose packing removed and another arterial bleeder located and ligated. Cellulose packing soaked in thrombin was spread out over the surface of the cavity and was tightly packed into the cavity with a mesh plain gauze packing making a Mikulicz type pack. No further bleeding occurred after this procedure. On Feb. 5, 1947, the packing was removed and the cavity inspected. The cavity in the liver was filled with bile stained packing. Blood had impregnated only the top packing suggesting that the bleeding had completely stopped. When the packing was removed healthy granulations were visible in the wall of the large cavity in the liver, measuring about 1.5 cm. in depth and 6 to 8 cm. across. What appeared to be an open biliary duct was visualized at the bottom of the cavity. No effort was made to suture this for fear of starting more bleeding and the wound was left almost entirely open for drainage. No further bleeding episodes occurred and the cavity gradually filled in. For about one month after the packing was removed there was bile drainage in decreasing amounts. By April 9, 1947, the wound was entirely closed.

During his hospitalization his health and strength. At one period, he was gaining

unable to determine the size of the liver because of the scars in the area but percussion suggests that it is still slightly enlarged.

DISCUSSION

The subject of hemorrhage into the biliary tract following trauma known as traumatic hemobilia has been recently discussed in the literature by Dr. Philip Sundblom* of Stockholm, Sweden. He reported that such a condition has been previously observed only rarely. He was able to find only nine cases in which trauma to the liver had resulted in hemorrhage to the biliary tract. The diagnosis in the majority of the reported cases has been by supposition and this case, which was so definitely proved by the numerous surgical procedures, seems quite unique. The characteristic picture of gastrointestinal hemorrhage associated with simulated biliary colic and preceded by trauma to the liver should make one suspect the true diagnosis. In the cases collected by Sundblom the bleeding was generally transient. Our case illustrates the fact that extravasation of blood into the biliary system can occur from deep laceration of the liver.

Editorial

Mixed Tumors of Anlage Origin

VARIOUS suggestions have been advanced to explain the structure and cellular origin of anlage tumors of the salivary gland type that formerly were called "mixed tumors of the salivary glands." This older name implies their origin from two of the germ layers and a close relation to salivary glands. Recently Helliwig¹ reviewed the principal theories of the cellular origin of these neoplasms and concluded that they are derived from misplaced elements of the notochord. A group of salivary gland tumors segregated by Stewart, Foote, and Becker² was designated by them as "muco epidermoid" tumors. They implicated the salivary gland ducts as the anatomic site of origin. The name "adenomyoepithelioma of the palatal mucous glands" was applied by Bauer and Fox³ to another group. These were believed to arise from cells lining the intercalated ducts of the palatine mucous glands. Further inquiry into the cellular structure of the so called salivary gland tumors led to the conclusion that they are derived from embryonal rests of the ectoderm.⁴ This concept affords a reasonable explanation of the varied cellular patterns and behavior of these growths.

Cells left over in the process of evolution of the individual are present at many sites. These cells usually remain dormant. If the cell rests commence to proliferate, they may reproduce a complete pattern forming an aberrant organ, or they may develop into a so called benign neoplasm or they may form a cancerous growth. A neoplasm of cell rest or anlage origin imitates the pattern of the tissue or organ in the formation of which the cell rest would have participated. Depending on the stage of development of the individual at the time when the cells became segregated these growths may be simple neoplasms mimicking a tissue or they may be mixed tumors mimicking an organ, or teratomas mimicking an individual.⁵

A familiar example of tumors of anlage origin mimicking a tissue is the adamantinoma. Such neoplasms usually occur about the jaw and occasionally at the base of the skull in the region of the sella turcica. Rarely an adamantinoma has been observed also in other locations like the tibia.⁶ Adamantinomas are composed of ameloblasts—cells which form the enamel of the tooth. The ameloblasts mimic the structure of a budding enamel body. The adamantinoma or ameloblastoma is an ectodermal epithelial growth the supporting stroma of which is provided by the surrounding connective tissue.

The anlage tumors of the salivary gland type are examples of mixed tumors mimicking organs. Such growths usually occur along the lines of fusion of embryonal facial fissures where salivary glands are numerous. They have also been observed at sites distant from the head where salivary glands do not usually occur. Since these growths do not reproduce nor imitate the

normal structure of the salivary glands, there is no reason to assume other than an incidental relation between them and the salivary glands. This is further evidenced by the occasional extension of the growth into the nearby glandular tissue without disturbing or distorting the pattern of the gland. This relation suggests a juxtaposition rather than derivation from the salivary gland.

The differences in structural patterns between the adenocarcinomas and the anlage tumors of the salivary gland type may be attributed to at least two factors. One of these is the influence of the environment on the neoplasms in their respective sites. The other is the stage of evolution of the cell rests at the time when they became separated from the ectoderm. Adenocarcinomas are apparently of more recent genetic origin, hence their simpler range of variation in cellular structure. The anlage tumors of the salivary gland type are genetically older. The stroma in these growths is a part of the neoplasm. The groups of cells from which these neoplasms are derived must have separated from the ectoderm at the stage when they had as yet not acquired their dominant characters as ectodermal and mesodermal cells, hence their ability to differentiate into both ectodermal and mesodermal tissues. In these growths there are marked variations in the cellular patterns. There are present in varying proportions undifferentiated and differentiated epithelial elements, embryonal connective tissue, adipose tissue, spaces lined by endothelium, young and adult connective tissue, hyaline cartilage and osseous tissue. There may be observed an apparent transformation of ectodermal elements into mesodermal tissue elements, such as the gradual transition of epithelial cells into cells of hyaline cartilage.

Among 38 anlage tumors of the salivary gland type observed at the University of Oklahoma Hospitals, 29 were located in or about the parotid glands, 6 in or about the submandibular glands, and 3 in the maxilla.⁷ These neoplasms also occasionally occur on the head at or near embryonal facial fissures at sites where there are usually no salivary glands, such as about the eyes.⁸ They have also been observed in locations distant from the head. According to a recent survey, about 20 such neoplasms have been reported. Of these 12 were on the upper extremities, 3 on the lower extremities, and 1 each in the inguinal region, the vulva, in the sternum, and in the mammary gland. Recently 3 additional tumors about the eyes and 3 which were distant from the head have been observed, one over the sternum, one in the mammary gland, and one on the back. That on the back is believed to be the first anlage tumor in this location.⁹

In the growths occurring at sites distant from the head there is a less complicated pattern with a predominance of the epithelial elements. There is also less tendency to the production of cartilage and other mesodermal tissue elements. These differences in cellular patterns may be attributed to local influences on the anlage from which the growths are derived. On close scrutiny of the microscope structure, however, no fundamental difference is disclosed between the anlage tumors of the salivary gland type occurring in sites usual for these growths and those occurring elsewhere. The morphologic observa-

tions, as a whole, reinforce the concept of the anlage origin of these growths and support the idea that the proximity to salivary glands is incidental rather than essential. A suitable designation, therefore, for such a growth is "mixed tumor of anlage origin" with mention of the site where it happens to occur.

—Bela Halpert

REFERENCES

- 1 Hellwig C Alexander Mixed Tumors of the Salivary Glands Arch Path 40 110
1945
Epidermoid Tumors of Sal
na (Cylindroma) of Palatal
and Craniofacial regions.
- 2 Halpert, Bela Morphologic Aspects of Cancer Research Scient Monthly 68 221 4
1949
- 3 Halpert Bela and Dohn H Halbj Adamantinoma in the Tibia Arch Path 43 313
317, 1947
- 4 Halpert, Bela, and Foot Charles D Anlage Tumors of the Salivary Gland Cancer
Research 7 316-320 1947
- 5 Halpert Bela Salivary Gland Tumors in Rare Sites Report of Two Cases, Yale J
Biol & Med 5 409-411 1943
- 6 Halpert Bela and Hackney Victor C Anlage Tumors of the Salivary Gland Type in
Unusual Site SURGERY (In press)

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